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SKYROCKETING PRESCRIPTION DRUG PRICES

HEARINGS

BEFORE THE

SPECIAL COMMITTEE ON AGING
UNITED STATES SENATE

ONE HUNDRED FIRST CONGRESS

FIRST SESSION

WASHINGTON, DC

ARE WE GETTING OUR MONEY'S WORTH?
JULY 18, 1989

TURNING A BAD DEAL INTO A GOOD DEAL
NOVEMBER 16, 1989

Serial No. 101-14

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PRESCRIPTION DRUG PRICES: ARE WE GETTING OUR MONEY'S WORTH?

TUESDAY, JULY 18, 1989

U.S. SENATE,
SPECIAL COMMITTEE ON AGING,
Washington, DC.

The committee met, pursuant to notice, at 9:38 a.m., in room 628, Dirksen Senate Office Building, Hon. David Pryor (chairman of the committee) presiding.

Present: Senators Pryor, Shelby, Reid, Graham, Kohl, Cohen, Pressler, Grassley, Wilson, Simpson, Warner, and Kassebaum.

Staff present: Portia Porter Mittelman, staff director; Christopher C. Jennings, deputy staff director; David Schulke, chief of oversight; and John Monahan, investigator.

OPENING STATEMENT BY SENATOR DAVID PRYOR, CHAIRMAN

The CHAIRMAN. Good morning, ladies and gentlemen. This morning we begin a series of hearings that will explore three questions: One, what is the value of the prescription drug products we buy? Two, what are the benefits of these drugs as compared to their costs? And three, what can we do to make certain that we are paying a fair price? From the tiniest baby in America to the oldest citizen in our country, it is an issue that affects all of us.

First, I must say I'm sorely disappointed that we will be unable to adequately pose and ultimately answer these questions this morning because those companies that manufacture these drugs chose not to come to this hearing. They chose not to testify today even though we changed the timing of this hearing to accommodate the conflict of schedules of company spokespersons. They should, it would appear, want to be present to make themselves available to be a part of this dialog

Many of these companies who proclaim the benefits their drugs produce evidently refuse in public to talk about the profits that they reap. When it comes to boasting of their profits to Wall Street, the drug companies can be heard loud and clear, but they are awfully quiet when it comes to discussing the prices they charge on Main Street.

Only one of the 18 drug manufacturers that was invited is present today. Those invited today who are not here include: American Home Products Corp., Barr Laboratories, Bolar Pharmaceutical, Eli Lilly and Co., Geneva Generics, Inc., Glaxo, Inc., Marion Laboratories, Inc., Merck Sharp and Dohme, Pfizer, Rugby-Darby Group Companies, Inc., Schein Pharmaceutical, Schering-Plough

Corp., Smithkline Beckman Corp., Squibb Corp., Syntex Corp., The Upjohn Co., Vitarine Pharmaceuticals, and Warner Chilcott Laboratories.

I also believe the public should hear some of the firms' reasons for not appearing today. One reason, in an answer to my request was, "We believe that a hearing is not an appropriate forum in which to elucidate the very complex issues you raise." I wonder what the proper setting might be?

The second response that we got, and another I think you might be interested in: "The data you have requested on international prices are of limited analytical value." Now, I appreciate this response, trying to save our time, but I would also think the Committee would like to draw its own conclusion as to the value of this data.

Why do companies fear this particular public forum? These companies are strong, their profits are phenomenal. Let me read you what Wall Street is saying about these manufacturers. The Wall Street analysts at Hambrecht & Quist, Inc. said: "The profitability for the pharmaceutical industry has been consistently above that of the Standard and Poors 400, the main industrial sector of the market. If anything, this gap has widened over the past 10 years."

An analysis of industry profit data shows that the top manufacturers earned steadily increasing profits from 1986 through 1988, while their taxes actually went down during the same 3 years. This data shows that 11 top U.S. drug makers had an average stock earnings record better than 78 percent of American manufacturers.

Wall Street investment analysts, at Le Rothschild, Unterberg, and Towbin, said as recently as 1986:

> Since the late 1970s—but most noticeably in the last 3 years— pricing has become the major force in generating revenue growth for drug companies.

Why are these companies relying on price increases when they could be generating new sales with breakthrough drug products that actually heal the sick? Here's what the London Economist said in 1987:

> Most recent drug product launches have been "me-too" drugs which do not find new markets but simply provide substitutes for older products. They are viewed with increasing impatience by regulatory authorities, who see "me-toos" as unnecessarily fancy versions of adequate drugs.

The Economist further summarizes the problem for the drug companies this way: " 'Me-too' drug products are evidence of the drug companies' poverty of inspiration. While 'me-toos' may keep the companies' new product rosters looking healthy, their value to the consumer is open to question."

Now, to be fair, since the drug companies have refused to show up this morning, I will make one of their arguments for them. Research and development for new drugs is very expensive. And I agree. I think all of us do. On the chart [1] farthest to my right you will see one of the industry's latest advertisements, claiming that it costs $125 million to bring what they call a new drug to the market. This is one of a series of advertisements the Pharmaceutical Manufacturers Association is running.

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[1] See appendix 1, p. 339 for charts used in hearing.

Now, the point of this ad is to remind us that the high prices we pay for many prescription drugs are our investment in expensive research and development, or R&D as our tax laws label it.

I looked into the research this ad is based upon, though, and what the ad doesn't tell us about the new drugs they say cost $125 million to develop is that they represent only about one-fourth of new drugs brought to market by the drug companies. The other 75 percent of the so-called new drugs are actually streamlined versions of old drugs; thus, the label of me-too drugs.

The drug companies want us to believe that it takes $125 million to invent the next penicillin, or a cure for AIDS, or treatment for Alzheimers. All of us would consider a cure for these diseases a bargain at $125 million. I would like to take this opportunity to personally recognize the hundreds of those scientists, researchers, and technicians who daily fight the battle against such dreaded diseases.

But let's be honest with each other. Most new drugs are not breakthrough drugs. In fact, for every breakthrough product they invent, American drug companies bring 24 drugs to the market that provide little or no therapeutic gain over already-marketed drugs, according to ratings by the Food and Drug Administration.

Some people call these "me-too" drugs because they represent a company's attempt to jump into a profitable market for an existing drug therapy. If we look at the next chart, closest to me, the one labeled the "The Me-Too Factor," you will see that of the 348 new drugs brought to the market by the top 25 drug companies between 1981 and 1988, 292 of these 348 were classified by the Food and Drug Administration in the so-called "C" category.[2]

These companies produced a total of only 12 "important" new drugs, and 44 other products that make what FDA called a "modest contribution" to existing therapies. This translates to the fact that 84 percent of new drugs fall into FDA's "C" category, making "little or no" contribution to anything but the bottom line of a profit and loss statement.

The story is the same if you consider the value of the minority of new drugs, called "new molecular entities," referred to by the PMA, the Pharmaceutical Manufacturers Association, in their ads. About 60 percent are rated by FDA as me-too drugs with questionable benefits no matter how you slice it.

And folks, the situation gets worse because the prices established by drug companies for these modest and insignificant new drugs are anything but modest and insignificant in their pricing. The next chart, labeled "Drug Price Increases Outpace Inflation, 1981 to 1988," graphically illustrates how price increases by drug manufacturers outpaced the general inflation rate. In fact, from 1981 through 1988 the prescription drug inflation rate of 88 percent dwarfed the general inflation rate of 28 percent. The Wall Street investment analysts I mentioned before, Hambrecht & Quist, Inc., said last year: "New drugs are priced higher, in most cases substantially higher, than older medications."

---

[2] See appendix 1, p. 339 for charts used in hearing.

Manufacturers claim they need exorbitant prices in order to pay for their research and development expenses. Once again, let's be honest with one another. The American public is footing much of the bill for these companies' research and development costs.

Fact: Through the use of the R&D tax credits, special expensing and allocation rules, and the possession tax credit for Puerto Rico, drug companies annually receive tax breaks well in excess of $1 billion. For example, in 1985, even before the 1986 tax bill, drug companies received R&D-related tax breaks of almost $1 billion, representing more than 24 percent of their tax expenditures.

Fact: Between 1984 and 1987, the American pharmaceutical industry's effective tax rate decreased by more than 27 percent.

Fact: The 1986 tax law provided even more liberal incentives for the drug companies in research and development and other tax breaks and subsidies.

Fact: Since 1981, R&D tax credits for just two drug companies in America added up to $93 million.

So let's be honest with ourselves. When the pharmaceutical manufacturers talk about research and development, let's talk about who really is paying for the research and development costs, the American taxpayer and the American consumer.

American physicians often do not realize that new drugs cost more than the drugs they are already buying. In fact, I am told that the costs of these new and largely duplicative drugs contributed significantly to CBO's recent increase in cost estimates for the Medicare drug benefit program. We have a lot to learn about drug companies in this country.

What do people pay for the same drugs in other countries? How are Americans faring, for example, with our European friends? Let's take a look at the next bar graph, "International Drug Price Comparison, Weighted Average Retail Price Per Brand Drug, 1987." It shows that Americans pay as much as five times more than European citizens pay for the same prescription drugs.

Here in the United States the price you pay for a prescription drug depends on who you are and what kind of deal you can strike with the manufacturer. The final chart, entitled "Range of Market Prices for Prescription Drugs," shows how hospitals and the Veterans Administration get the best prices. Who gets the worst prices? Medicaid, Medicare, and the general public buying at the pharmacies get the worst price, because the pharmacists have to pay the very highest price.

I have graphically, I hope, something else to illustrate here. After all the charts and after all the graphs and all the words, it comes down to this. We have here the published list price for Motrin, for example. Here's that published list price. I'll put that right there.

[Demonstrating bottle of Motrin.]

The **Chairman**. Here's what Medicare would pay for that Motrin: $29. Here's what the hospital pays, $8 for the same bottle. Here's what the Department of Veterans Affairs pays, $5. So we see a vast range of price variation between the various prices that the drug manufacturers charge to these prospective customers.

Let me also state that the local pharmacist at the local drug store, the person who is out there in the trenches every day, in the foxhole, selling drugs to Aunt Minnie and Cousin Joe and whoever, this druggist is the one who has to almost on a weekly or monthly basis tell those consumers that their prices are going up yet once again. Now, why is it that we're seeing those tremendous price increases when the druggist himself, as we will see later in another chart, is receiving only a few pennies, only a few cents more, for a prescription which is backed up by Medicare and other governmental programs?

We have a lot of questions to answer. We have several Senators here. I will use the early bird rule. I will call on Senator Wilson of California first.

[The prepared statements of Senator Pryor, Senator Heinz, and Senator Bradley follow:]

DAVID PRYOR, ARKANSAS, CHAIRMAN

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United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

SENATOR DAVID PRYOR, CHAIRMAN

OPENING STATEMENT

"PRESCRIPTION DRUG PRICES: ARE WE GETTING OUR MONEY'S WORTH?"

SENATE SPECIAL COMMITTEE ON AGING HEARING

JULY 18, 1989

This morning we begin a series of hearings that will explore three questions: (1) What is the value of the prescription drug products we are buying; (2) What are the benefits of these drugs as compared to their costs; and (3) What can we do to make certain that we are paying a fair price.

First, I must say that I am sorely disappointed that we will be unable to adequately pose and ultimately answer these questions because those companies that manufacture these drugs chose not to come to this hearing. They chose not to testify today even though we changed the timing of this hearing to accommodate the conflict of schedules of company spokespersons. They should want to be present to make themselves available to be a part of this dialogue.

Many of these companies who proclaim the benefits they produce evidently refuse in public to talk about the profits they reap. When it comes to boasting of their profits to Wall Street, the drug companies can be heard loud and clear, but they are awfully quiet when it comes to discussing the prices they charge on Main Street.

Only one of the 18 drug manufacturers that was invited is present today. The firms invited today are:

AMERICAN HOME PRODUCTS CORP.
BARR LABORATORIES
BOLAR PHARMACEUTICAL
ELI LILLY AND COMPANY
GENEVA GENERICS, INC.
GLAXO INC.
MARION LABORATORIES, INC.
MERCK SHARP & DOHME
PFIZER INC.
RUGBY-DARBY GROUP COMPANIES, INC.
SCHEIN PHARMACEUTICAL, INC.
SCHERING-PLOUGH CORPORATION
SMITHKLINE BECKMAN CORPORATION
SQUIBB CORPORATION
SYNTEX CORPORATION
THE UPJOHN COMPANY
VITARINE PHARMACEUTICALS
WARNER CHILCOTT LABORATORIES

I also believe the public should hear some of the firms' reasons for not appearing today:

> "We believe that a hearing is not an appropriate forum in which to elucidate the very complex issues you raise." (Since when is a public hearing not an appropriate forum to examine complex issues?)

> "The data you have requested on international prices are of limited analytical value." (Although I appreciate them trying to save us time, I would like the Committee to draw its own conclusion.)

Why do companies fear this public forum? The companies are strong; their profits are phenomenal. Let me read you what Wall Street is saying about these manufacturers. The Wall Street analysts Hambrecht and Quist say:

> "The [profitability] for the pharmaceutical industry has been consistently above that of the [Standard and Poors] 400, the main industrial sector of the market. If anything, this gap has widened over the past ten years."

An analysis of industry profit data shows that the top manufacturers earned steadily increasing profits from 1986 through 1988, while their taxes went down during the same three years. This data shows that eleven top U.S. drug makers had an average stock earnings record better than 78% of American manufacturers.

Le Rothschild, Unterberg, and Towbin, Wall Street investment analysts, said in 1986:

> "Since the late 1970s - but most noticeably in the last three years - pricing has become the major force in generating revenue growth [for drug companies]..."

Why are these companies relying on price increases, when they could be generating new sales with breakthrough drug products that heal the sick? Here's what the London Economist said in 1987:

> "Most recent [drug] product launches have been 'me-too' [drugs], which do not find new markets, but simply provide substitutes for older products. They are viewed with increasing impatience by regulatory authorities, who see 'me-toos' as unnecessarily fancy versions of adequate drugs."

The Economist summarizes the problem for the drug companies this way:

> "'Me-too' [drug] products are evidence of the drug companies' poverty of inspiration... While 'me-toos' may keep the companies' new products rosters looking healthy, their value to the consumer is open to question."

Now, to be fair, since the drug companies have refused to show up today, I will make one of their arguments for them. Research and development for new drugs is very expensive. On my right is one of the industry's advertisements, claiming that it costs $125 million to bring what they call a "new drug" to market.
[REFER TO APPENDIX B OF AGING COMMITTEE STAFF BRIEFING PAPER]

The point of the Ad is to remind us that the high prices we pay for many prescription drugs are our investment in expensive research and development -- or "R&D" as our tax laws label it.

I looked into the research this ad is based on, though, and what the ad doesn't tell you is the "new drugs" they say cost $125 million to develop represents only about one-fourth of new drugs brought to market by the drug companies. The other 75 percent of so-called new drugs are actually streamlined versions of old drugs. Thus, the label of "me-too" drugs.

The drug companies want us to believe that it takes $125 million to invent the next penicillin, or a cure for AIDS, or treatment for Alzheimers' disease. All of us would consider a cure for these diseases a bargain at $125 million. And, I would like to take this opportunity to personally recognize and praise the long hours and hard work put in by researchers, scientists, and technicians who daily fight the battle against such dreaded diseases.

But, let's be honest here. These drugs are not "breakthrough" drugs. In fact, for every breakthrough product they invent, American drug companies bring 24 drugs to market that provide little or no therapeutic gain as rated by the Food and Drug Administration.

Some people call these "me-too" drugs because they represent a company's attempt to jump into a profitable market for an existing drug therapy. If we look at the next chart [REFER TO APPENDIX A OF AGING COMMITTEE STAFF BRIEFING PAPER], you will see that of the 348 new drugs brought to market by the top 25 American drug companies between 1981 and 1988, 292 were "me-too" drugs.

These companies produced a total of only 12 "Important" new drugs and 44 other products that make what FDA calls a "Modest" contribution to existing therapies. This means 84% of new drugs fall into FDA's "C" category, making "little or no" contribution to anything but the bottom line of a profit and loss statement.

The story is the same if you consider the value of the new drugs referred to by the PMA in their ad: about 60% are rated by FDA as "me-too" drugs with questionable benefits no matter how you slice it.

But it gets worse, because the prices established by drug companies for these "modest" and "insignificant" new drugs are anything but "modest" and "insignificant". Chart 3 [REFER TO APPENDIX D OF AGING COMMITTEE STAFF BRIEFING PAPER] graphically illustrates how drug price increases outpace the general inflation rate. From 1981 through 1988, the prescription drug inflation rate of 88 percent dwarfed the general inflation rate of 28 percent. The Wall Street investment analysts I mentioned before, Hambrecht and Quist, said last year:

> "New drugs are priced higher, in most cases substantially higher, than older medications."

Manufacturers claim they need exorbitant prices in order to pay for their research and development expenses. The truth is, though, that the American public is footing much of the bill for companies' R&D costs.

> FACT: Through use of R&D tax credits, special expensing and allocation rules and the possession tax credit, drug companies annually receive tax breaks well in excess of $1 billion. (For example, in 1985, drug companies received R&D related tax breaks of almost $1 billion, representing more than 24 percent of such tax expenditures).
>
> FACT: Between 1984 and 1987, the pharmaceutical industry's effective tax rate decreased by more than 27 percent.
>
> FACT: The 1986 tax law provides even more liberal incentives for drug companies.
>
> FACT: Since 1981, R&D tax credits for just two drug companies added up to $93 million.

A survey done by the Leonard Davis Institute of Health Economics at the University of Pennsylvania found that American consumers do not realize that new drugs cost more than the drugs they are already buying. In fact, I am told that the costs of these new and largely duplicative drugs contributed significantly to CBO's recent increase in cost estimates for the Medicare drug benefit. We have a lot to learn about drug companies in this country.

What do people pay for the same drugs in other countries? Take a look at the chart on my right [REFER TO APPENDIX F OF AGING COMMITTEE STAFF BRIEFING PAPER], titled "International Drug Price Comparison". It shows we pay as much as five times more than European citizens pay for prescription drugs.

And here in the United States, the price you pay for a prescription drug depends on who you are and what kind of a deal you can strike with the manufacturer. The final chart [REFER TO APPENDIX H OF AGING COMMITTEE STAFF BRIEFING PAPER] entitled "Range of Market Prices for Prescription Drugs" shows how hospitals and the Veterans' Administration get the best prices, and Medicaid, Medicare and the public buying at pharmacies get the worst prices, because the pharmacies have to pay high prices.

We'll be learning a lot more about these and other issues from our witnesses today. I look forward to hearing from them and beginning the process toward assuring we as a nation are getting our money's worth from our investment in prescription drugs.

NEWS FROM
SENATOR JOHN HEINZ
SPECIAL COMMITTEE ON AGING

Senate Hart 628 Washington, D.C. 20510-6400 (202) 224-1467

July 18, 1989

Madelyn Glist
(202)224-1467

OPENING STATEMENT SENATOR JOHN HEINZ (R-PA)
SENATE AGING COMMITTEE HEARING ON PRESCRIPTION DRUG COSTS
18 JULY 1989

Mr. Chairman, I too am concerned about the potentially oppressive costs of prescription drugs for America's aged and thank you for calling this hearing today.

A few weeks ago, an 82-year-old constituent in New Cumberland, Pennsylvania wrote me about the burden of paying for the 100 pills she must take every month. Even with a medigap policy, Mrs. C writes, she pays hundreds of dollars out-of -pocket annually for drugs, and the cost creeps up by 10 percent or more each time she gets a refill.

Mrs. C is typical of millions of older Americans whose fixed, limited incomes increasingly are eroded by rising drug costs. Of the $9 million seniors spent for prescription drugs in 1986, $7.3 million -- or more than 4 out of every 5 dollars -- came from their own pockets.

By including a prescription drug benefit in the Medicare Catastrophic Act, Congress acknowledged the considerable burden of drug costs on the elderly, a burden that studies have shown actually prevents many seniors from getting the medications they need. As currently structured, more than 5 million elderly, each of whom presently spends over $600 a year on medication, would be helped by this benefit.

I am concerned over new estimates from the Congressional Budget Office (CBO) that suggest the prescription drug benefit is too costly for the government to finance with current revenues. As the principle author of this legislation, I remain convinced that the benefit not only is necessary, but that it is financially feasible. I have asked CBO to revisit their calculations.

In addition to the financial protections provided under the drug benefit, the Catastrophic law also establishes a unique, nationwide tracking and reviewing system that allows pharmacists to monitor the prescription drug regimens of Medicare beneficiaries. More than 250,000 elderly are hospitalized for adverse drug reactions or side effects from over-the-counter drugs each year. The Drug Utilization Review (DUR) program can save both lives and dollars by preventing such hospitalizations.

Senator Wilson and I have introduced legislation, S. 859, to fine-tune what we believe are some of the shortcomings of the DUR program as written into Catastrophic, including safeguarding the confidentiality of data and making better use of existing technology from the Department of Defense. I hope we will be able to deal with these recommendations as part of the reconciliation process.

(over)

Mr. Chairman, on the issue of fine-tuning, you have joined Senator Wilson and me in expressing some serious concerns about the Health Care Financing Administration's Request for Proposal (RFP) for the DUR system. HCFA's vision of a DUR falls far short of Congressional intent and underestimates the technological feasibility of a comprehensive system. The General Accounting Office (GAO) is about to release a report on this subject. I would hope that Acting Administrator Hays will be open to amendments to the RFP as called for by the GAO findings.

Congress has applied cost containment measures to hospitals and physicians under Medicare. There is no question that drug costs deserve similar evaluation and that Congress may need to legislate to control the rate of increases. Today's hearing is an important step in evaluating the extent of the problem and the relative weight of the causes. Again, I commend you for bringing us together this morning and would urge you to schedule a second hearing on the DUR in the near future.

SENATOR BILL BRADLEY TESTIMONY
PRESCRIPTION DRUG HEARING
SENATE SPECIAL COMMITTEE ON AGING
JULY 18, 1989

Bill Bradley

Mr. Chariman, I thank you for holding this hearing today. Prescription drugs represent a major and growing cost for the Nation's elderly. And they provide significant benefits in terms of length and quality of life.

Mr. Chariman, we have an enormous task before us -- how can you contain rising health care costs while at the same time improve the quality of health care provided to senior citizens? I believe the prescription drug benefit adoption last year as part of the Medicare Catastrophic Coverage Act was a good step in protecting the elderly from health care costs. But clearly more will need to be done in the years ahead.

I have a couple of questions that I would like to submit for the record to Louis B. Hays, the Acting Administrator of the Health Care Financing Administration.

As a general rule, what are the costs to the health care system and benefits to consumers to treat disease conditions with drugs rather than surgery or hospitalization? Can you identify drugs which have saved Medicare money because they have replaced surgery or hospitalization? Can these savings be quantified? Are there drugs that cost Medicare money and do not demonstrably improve the quality of life of Medicare beneficiaries?

There are many ways to control costs for goods and services, whether it be through regulatory control, the free market or public ownership of a product. In the US, we have a system of patented brand name drugs and generic drugs. We often have a number of drugs in the same therapeutic category used to treat a particular condition. How effective is our current system of generic/brand name drugs in controlling costs? What is the impact on costs and on benefits to consumers when there are only several brand name drugs available to treat a specific disease?

STATEMENT OF SENATOR PETE WILSON

Senator WILSON. Mr. Chairman, thank you very much. I must say that was a remarkable opening statement. I think it reveals the need for the hearing. I commend you for conducting it.

Mr. Chairman, I would like to say at the outset that I am happy to be able to welcome a constituent, Dr. George Rathmann, chairman of the board of Amgen, Inc., a company from Thousand Oaks, CA. Amgen is a truly significant entrepreneurial biotechnology firm, one really entering the market, and one that has gained great national attention in recent weeks with the Food and Drug Administration's approval of Epogen, its first commercial product and one that provides treatment of the severe anemia often associated with chronic kidney failure.

So if you're suffering from a lack of witnesses in other areas, you have one here that I think will be both relevant, and one whom I am pleased to introduce to the committee.

I will be required to be absent through a part of the testimony in order to be on the floor for the State authorization bill. But let me just say that the steady and continued growth in prescription drug costs, as you have rather dramatically indicated in one of your charts, not only significantly outpaced the rate of the general inflation, but also significantly the cost of both hospital and physician services. Inflation in prescription drug prices is of great and mounting concern in both the public and the private sectors. For many businesses the cost of prescription drug coverage is the fastest growing component of their health benefit packages with the exception of what they provide by way of mental health and substance abuse coverage.

The continued escalation of prescription drug prices has particular relevance to the Federal Government, as you have indicated, as it prepares to implement a comprehensive outpatient prescription drug program for elderly Americans under the Medicare Catastrophic Coverage Act. In anticipation of the Medicare prescription drug benefit, Mr. Chairman, we are indeed well-advised to explore the factors behind prescription drug pricing increases and to examine the means of obtaining prescription drugs at the best possible price.

One cannot help but be struck by the data to be shown this morning, some of which you have shown in your opening statement, that demonstrate the wide range of market prices paid for brand name prescription drugs. As the data will show, the Department of Veterans Affairs, for example, obtains prescription drugs at a significantly lower cost than those expected to be paid by Medicare once the drug benefit is implemented.

And while differences exist in the Department of Veterans Affairs and the Medicare Program in terms of their respective prescription drug purchasing abilities, I believe we must thoroughly explore the extent to which Medicare can organize itself to obtain the best possible price for prescription drugs.

At the heart of this hearing, Mr. Chairman, is the question of what can be done to restrain the costs of prescription drugs. Rising drug prices alone, however, do not tell the whole story behind overall prescription drug expenditures. The misutilization and inappropriate prescription of drugs play a role as well. Therefore we also must vigorously explore other cost containment strategies to rein in prescription drug expenditures.

In this regard it is essential that Congress take full advantage of technology to monitor the utilization and appropriateness of outpatient prescription drugs. Inappropriate and excessive prescriptions are particularly a problem for the elderly who, given the greater likelihood of being under the supervision of more than one physician and of taking multiple medications, are at greater risk of adverse drug reactions and interactions. In a report issued by this committee last year, as many as 120 million drug prescriptions for older Americans may have been inappropriate, at a cost of over $2 billion for the drugs themselves. By preventing inappropriate and excessive drug prescriptions, a prospective drug utilization review system will result in a substantial financial savings, but more important by far, in avoidance of inappropriate and perhaps harmful medication. While considerable savings will result due to the discontinuation or modification of drug prescriptions, even greater savings will come through avoiding the unnecessary and costly drug therapy-related hospitalizations and remedial care that result from this inappropriate drug prescription. And most importantly, obviously, drug utilization review will save tens of thousands of older Americans from the needless pain and suffering that comes from adverse drug reactions and interactions.

Recognizing the potential of drug utilization review, Congress directed the Department of Health and Human Services to implement a drug utilization review system as part of the new Medicare prescription drug benefit.

Given my belief in the potential of drug utilization review and concerns that the Health Care Financing Administration's drug utilization review implementation plans were not consistent with Congressional intent, I authored legislation to clarify requirements of the drug utilization review program to ensure a comprehensive state-of-the-art system with adequate privacy and confidentiality safeguards.

I am very pleased that you, Mr. Chairman, and the ranking member, Senator Heinz, have joined me in sponsoring this legislation and I'm confident that prospective, comprehensive drug utilization review will play a major role in our efforts to restrain the costs of Medicare's prescription drug benefit.

In closing, Mr. Chairman, I look forward to this Committee's examination of prescription drug manufacturers' pricing practices. It is clear that as the Federal Government becomes a major purchaser of prescription drugs through the Medicare Program, we must explore strategies for being a prudent and efficient buyer of such drugs.

In addition, I am hopeful that in the course of considering the broad question of controlling costs of Medicare's prescription drug benefit, this Committee will have the opportunity in the future to fully explore drug utilization review systems' potential to save millions of dollars in unnecessary Medicare costs and to save thousands of elderly Americans from needless pain and suffering.

Thank you.

The CHAIRMAN. Senator Wilson, thank you for your contribution.

Let us see if we can sort of lay down a little rule—I should have mentioned this earlier—if we can basically limit our opening statements to around 3 minutes. I hate to call time on my colleagues.

Senator Reid.

STATEMENT OF SENATOR HARRY REID

Senator Reid. Thank you, Mr. Chairman, for providing members of this committee with an opportunity to examine the current crisis in prescription drug costs. I'd like to acknowledge and extend my thanks to those witnesses that are going to appear.

We've all heard horror stories from people in our home States—the cost of monthly prescription drugs, suddenly, for example, increasing by two-fold, sometimes more than that; monthly prescription bills surpassing monthly food bills, or worse, supplanting food bills. Our elderly, in particular, must frequently choose between going hungry at the end of the month or refilling an essential but costly prescription.

As we discussed the various options for resolving the Medicare Catastrophic Act controversy, we considered reducing benefit levels in order to accommodate lower taxes for seniors. One benefit which would be sure to go would, of course, be the very expensive prescription drug benefit. If we do away with the Catastrophic Act, as I hope we do, or if we remove some of the more costly benefits, including the drug benefit, the need to stop rising drug costs will be all the more urgent. Affordable prescription drugs are vital to this Nation's health.

Mr. Chairman, in your opening statement you talked a lot about the profits that these companies make. And certainly this is something we must review closely, but we also must understand that these drug companies are getting little, if any, help from the Government. Any expenditures they make in developing these new drugs are coming from their own corporate accounts.

Mr. Chairman, several members of this committee—I know that there are some that have had family members that have been ill—have looked for these specialized drugs. Speaking for myself the last little bit, I have had some experience with this with two members of my family. Even though the drugs were very expensive, I was very happy that the manufacturing companies went the extra distance to come up with these specialized drugs.

So it's a difficult balance that we have to make, that is, to make sure that these companies have the proper incentives to continue trying to come up with some of these drugs, as you have illustrated, these new drugs.

I think it goes without saying, Mr. Chairman, that striking a balance is difficult. There is an entirely new subject that we need to be concerned about, and that is what the Government should be doing to help these companies develop these new products. We know that approximately one-third to one-fourth of all prescription drugs come from the rain forests, but yet the rain forests are being destroyed. So, this problem, even though it indicates that people are paying a lot for drugs—and I acknowledge that, and recognize that we have to do something to stop the spiraling costs—we also have to be concerned that there is an incentive for these drug companies to continue manufacturing and developing new products.

The CHAIRMAN. Thank you very much, Senator Reid.

Senator Grassley.

STATEMENT OF SENATOR CHARLES GRASSLEY

Senator GRASSLEY. Thank you, Mr. Chairman.

It appears that the recent reestimate of the cost of the Catastrophic Health Care Act shows that the surplus which we recently thought would be available for reducing the cost of that program to the taxpayers has disappeared. It was this surplus which was expected by some Senators to allow for the rollback in the rates so as to respond to the anger of those that will pay the supplemental premium. As I understand it the surplus disappeared because reestimates of the program costs showed that the prescription drug benefit was going to be much more expensive than we had anticipated.

I gather that the witness from the Health Care Financing Administration will say today that these Congressional Budget Office estimates, that have been back and forth on both ends of the court over the last month, are in keeping with what the Administration has been projecting for program costs for some time. It seems pretty clear that if drug prices escalate at a rapid rate, costs for the prescription drug program—assuming that we let it go into effect and that it is legislated—will present the Congress and the Administration with some unpleasant choices.

If the past is any guide to the future in our public life, all that we have to do, Mr. Chairman, is look to what has been happening to hospitals and doctors and the Medicare program in recent years to get an indication of what could be happening to drug manufacturers and pharmacists soon enough. And that is simply that when the Federal Government gets into a program, we have a way of helping drive up prices. Unfortunately, it's probably going to be difficult to achieve a consensus on this subject, because it is very controversial.

We have in our public debate on the subject sharply different views on the sources of the problem. On the one hand, some think that drug manufacturers have aggressively exploited their price policies, which leads to very rapid inflation in drug prices. Price increases in prescription drug products have run as high as 10 percent per year until just the last couple years and that's considerably in excess of the Consumer Price Index.

Now, manufacturer profits on prescription drug products run as high as 15 percent according to some information in recent reports from HCFA. On the other hand, it is clear that it is risky and expensive to develop new products. Relatively few of the great many products in which investments are made even make it into the market.

The new drug approval process, which is long and complicated, and contributes to delays in getting a new product to market, and after new drugs make it to the market they have patent protection for a relatively short period of time before cheaper generic drugs make it to the market. With possible commencement of the new

Medicare Prescription Drug Program, these issues all take on added importance. So, of course, it's very good that we hold this hearing. However, I don't know whether we can expect an answer to this problem as long as the Federal Government is a driving force in the cost of health care generally, and that's going to be as true as ever of this prescription drug program.

The CHAIRMAN. Senator Grassley, thank you very much.

Senator Shelby.

STATEMENT OF SENATOR RICHARD SHELBY

Senator SHELBY. Mr. Chairman, I'll try to be brief.

First of all I want to commend you, Mr. Chairman, for holding this hearing. I believe it's very important, and very important to the American people, and especially the elderly.

The issue of prescription drug pricing is of interest to all of us, but it impacts significantly upon the elderly, as the chairman has pointed out. Many seniors are not limited to just one medication each day, but are often taking several drugs at one time. For example, approximately 6.7 million elderly are taking three or more prescription drugs each day, or at one time, and one-third of the patients in nursing homes receive eight or more drugs daily, Mr. Chairman.

Also, we know that the seniors over age 65, only 12 percent of the population in this country, consumed 32 percent of the 1.53 billion prescriptions written in 1984. And that was in 1984; since then this figure has risen significantly. I'm sure, Mr. Chairman, that this figure has increased. Given these statistics, it is not difficult to imagine the tremendous price tag associated with obtaining medication in this country.

However, I also truly believe that drugs are a very cost-effective part of health care. A properly prescribed drug regimen can prevent the onset of more serious illnesses and can often preempt hospitalization. But soon many elderly individuals will be priced out of the market. I've talked to many local pharmacists in my State of Alabama who carry from month to month some of the elderly customers who cannot afford some of their prescriptions, knowing the serious consequences which may arise without the prescribed medication.

With passage of the Medicare Catastrophic Coverage Act last year, Medicare will cover a portion of the costs of prescription drugs. Therefore it is important to understand the pricing policies and develop mechanisms for cost containment before the program is fully implemented. I'm particularly interested in pricing differential practices, as you are, Mr. Chairman.

I'm anxious to hear from our distinguished panel of witnesses this morning, and I would particularly like to thank Mr. Rathmann for appearing before this committee. As the chairman mentioned, several other pharmaceutical manufacturers were invited but declined the offer. I think they should be here.

The CHAIRMAN. Thank you very much, Senator Shelby.

Senator Cohen.

STATEMENT OF SENATOR WILLIAM COHEN

Senator Cohen. Mr. Chairman, I have a very brief statement which I would like to insert in the record.

This hearing is important to the elderly, to the taxpayers, and certainly to the drug manufacturing industry itself, and I will deprive the waiting audience of further remarks from me so that we can move on.

[The prepared statement of Senator Cohen follows:]

Senator William S. Cohen

The Importance of Understanding Rising Prescription Drug Costs

I would like to commend the Chairman for holding a hearing on this very relevant subject.

Prescription drugs are becoming an increasingly important part of the medical care provided in this country. As the costs of medical care of risen dramatically, the nation has searched for more efficient and effective ways to provide care. Increasingly, we are finding it possible and beneficial to use prescription drugs as an alternative to some medical procedures. Prescription drug treatment has not only become a more comfortable form of treatment in some cases, but it is less costly. Patients benefitting from drug treatment may experience less pain and be able to return to normal daily routines quicker than they have in the past.

While prescription drug treatment may be a less costly form of treatment for certain ailments, the costs have still been rising. This is of particular concern to our elderly population who often have to bear the burden of paying for drugs. And, as the elderly consume a large portion of the prescription drugs purchased, it is they who are most adversely affected by the rising prices.

The high cost of prescription drugs is also becoming more of a concern to the government as we have decided to embark on a major expansion of Medicare. It is crucial for us to understand the nature of prescription drug pricing before we begin providing the prescription drug benefit through Medicare beginning in 1991. We are well aware of the difficulties we are having controlling the costs of Medicare. It is essential that government not add to the problem of medical care inflation because of our presence in the prescription drug marketplace. That will only make our health care woes worse. Today, we will learn how to obtain a favorable price for prescription drugs that benefits consumers and is fair to pharmacists and manufacturers.

The **Chairman**. Thank you very much, Senator Cohen.

Senator Kohl.

STATEMENT OF SENATOR HERBERT KOHL

Senator **Kohl**. Thank you, Mr. Chairman. I'd like to commend you for your leadership on this issue.

We have nothing short of a crisis, as we all know, in American health care costs. By and large it is those among us who are least fortunate and least able to pay who seem to bear the brunt of the costs. I've heard, as most people have, too many horror stories from senior citizens. In my own State of Wisconsin there's an elderly lady from Reedsburg who wrote in just last week and said, "I purchased 12 pills for $34 less 10 percent," and she said, "This is ridiculous, can't we do something about it?" And there's the pharmacist who tells about senior citizens doing without their prescriptions because they can't afford them, or those trying to make the prescriptions last longer by cutting their doses in half.

There is a pharmacist's cooperative that sent out prebid letters for competitive pricing on multisource, nongeneric drugs and didn't get one taker. They seem to be doing their share to reduce the price of the drugs to the consumer. Most pharmacists are even absorbing some of the costs, so what is the problem?

Well, I don't claim to understand everything about the pharmaceutical business, but I do understand on a fundamental and moral level that people have a right to quality health care and that millions of people on low and fixed incomes are getting squeezed out. I understand that Government has some responsibility with the public purse. As a major purchaser of health care, the Federal Government has to do the most it can with the least amount of money. That means getting a competitive price on prescription drugs.

As a businessman, Mr. Chairman, I know that business needs incentives to invest in things like research and development and to be innovative. I know that there are certain fixed costs that have to be covered, and I know that shareholders expect a certain return on investment. So I can appreciate the value of Federal incentives like patenting rights and research and development tax credits, as well as the importance of profitable marketing strategies. But how are all of these concerns balanced out there in the marketplace? Who is looking out after the concerns of the elderly woman from Reedsburg, WI? Who is asking if the product is worth the price, and who out there, Mr. Chairman, is setting the rules of the game?

I look forward to hearing the testimony of these witnesses in an effort to get a better sense of the answers to these big questions. Thank you, Mr. Chairman.

The **Chairman**. Senator Kohl, thank you very much.

Senator Pressler.

STATEMENT OF SENATOR LARRY PRESSLER

Senator **Pressler**. Mr. Chairman, in the interest of time I shall put my statement in the record. However, I want to commend you for holding this hearing.

Also I want to state that small, independent, small town pharmacists are not guilty of the price problem. They frequently are unable to obtain the same discounts that are available to large purchasing groups. They are at the mercy of the large companies. I believe this may be an example of large companies engaging in price fixing. We need to determine if that is the reason.

I commend the one company that has appeared here today. I hope we will have the cooperation of all manufacturing companies. Also, I note from the one chart here that American citizens are paying two to three times as much for their drugs than do people in the developed Western European nations. This is a surprise. We talk about the cost of medical care in this country; prescription drug costs are a critical part of the problem. I commend the chairman and the committee for its investigation of this problem.

[The prepared statement of Senator Pressler follows:]

PRESCRIPTION DRUG PRICING
STATEMENT FOR SENATE AGING COMMITTEE
JULY 18, 1989

LARRY PRESSLER

MR. CHAIRMEN: MANY THANKS TO THE CHAIRMEN FOR HOLDING THIS HEARING ON THE PRICING OF PRESCRIPTION DRUGS. I AM PLEASED THAT THE SENATE AGING COMMITTEE IS EXAMINING THE REASONS FOR THE HIGH COST OF PRESCRIPTION DRUGS.

MY CONSTITUENTS ARE CONTINUOUSLY REMINDING ME OF HOW EXPENSIVE IT IS TO PURCHASE MEDICATIONS. I UNDERSTAND THAT COSTS ARE HIGH. HOWEVER, I, LIKE MANY OTHERS, DO NOT UNDERSTAND THE COMPLEXITIES INVOLVED IN THIS ISSUE.

RETAIL PHARMACISTS ARE CONCERNED ABOUT THE COST OF PRESCRIPTION DRUGS. THE INDEPENDENT SMALL TOWN PHARMACISTS, IN RURAL SOUTH DAKOTA, ARE UNABLE TO OBTAIN THE SAME DISCOUNTS THAT ARE AVAILABLE TO LARGE PURCHASING GROUPS.

WE NEED TO EXPLORE THE INTRICATE, YET SENSITIVE DIMENSIONS OF ASSOCIATED WITH THE HIGH COST OF PRESCRIPTION DRUGS. I HOPE THAT TODAY'S HEARING WILL ENLIGHTEN US ON THE MANY FACETS OF THIS PROBLEM. I LOOK FORWARD TO HEARING THE TESTIMONY OF OUR EXPERT WITNESSES

The **Chairman**. Thank you, Senator Pressler.

Senator Warner.

STATEMENT OF SENATOR JOHN WARNER

Senator **Warner**. Thank you, Mr. Chairman. I'll submit my statement to the record.

I think that my colleagues have carefully summarized the problem. On the one hand you've got one of the strongest industries in America, one that is contributing in a positive way to our negative balance of payments, one that has attracted attention from all over the world because we are the world leader in producing some of the finest prescription drugs to care for the ill. On the other hand, we've got a segment of our society least able to pay that seems to be bearing a disproportionate burden of the costs.

It would be my hope that the expertise that these industrial giants have brought to bear on not only on the balance of payments but also the finest of drugs can now be turned to this question of marketing. Let that expertise try and guide the Congress in seeking a solution in this marketing problem rather than our striking out on our own in these uncharted waters. Clearly, there is a problem. Clearly, there is a solution. Help us find it.

[The prepared statement of Senator Warner follows:]

SENATOR JOHN WARNER
July 18, 1989
SPECIAL COMMITTEE ON AGING

"PRESCRIPTION DRUG PRICES: ARE WE GETTING OUR MONEY'S WORTH?"

MR. CHAIRMAN, I AM PLEASED THAT THE COMMITTEE IS TAKING THIS TIMELY ACTION IN EXAMINING PRICING PROCEDURES FOR PRESCRIPTION DRUGS. WITH THE ADVENT OF MEDICARE COVERAGE OF PRESCRIPTION DRUGS BEGINNING IN 1991 AND THE VAST OUTLAYS THIS WILL INVOLVE, WE MUST ENDEAVOR TO FULLY UNDERSTAND PRICING AND PRODUCTION POLICIES OF THE PHARMACEUTICAL INDUSTRY. WHAT, EXACTLY, ARE WE IN FOR - - CAN WE INDEED PROJECT THE ULTIMATE IMPACT ON THE MEDICARE TRUST FUNDS.

I UNDERSTAND THAT THIS IS MEANT TO BE AN INITIAL HEARING IN A LENGTHY OVERSIGHT INITIATIVE. THERE IS NO ACCOMPANYING LEGISLATION PROPOSING SOLUTIONS TO IDENTIFIED PROBLEMS. WE ARE HERE TO GET WHAT FACTS WE CAN TO BETTER ASSIST THE CONGRESS IN MEETING THE DEMANDS OF THE NEAR FUTURE.

I HAVE BEEN IMPRESSED WITH THE INFORMATION PROVIDED TO THE COMMITTEE BY THE DEPARTMENT OF VETERANS AFFAIRS (DVA). THROUGH BOTH OF THE DEPARTMENT'S PROCUREMENT ARMS - - THE DEPOT SYSTEM ACQUIRING BULK PHARMACEUTICAL COMMODITIES AND THE FEDERAL SUPPLY SCHEDULE SYSTEM DIRECTLY NEGOTIATING FOR PROPRIETARY AND GENERIC DRUGS --, DVA REPRESENTATIVES HAVE BEEN ABLE TO SECURE SIGNIFICANT PRICE DISCOUNTS.

DVA IS PRACTICING PROVEN MARKETPLACE SKILLS IN NEGOTIATING ON A COMPETITIVE BASIS WHEREVER POSSIBLE. THE KEY, OF COURSE INVOLVES COMPETITION AND VOLUME. WHAT THE COMMITTEE SEEKS TO EXAMINE IS WHETHER ON NOT THESE MARKETPLACE TECHNIQUES CAN BE ADAPTED FOR PURPOSES OF OTHER GOVERNMENTAL PROGRAMS, PRINCIPALLY MEDICARE.

THE EXAMPLE PROVIDED FOR THE COMMITTEE IN THE VITAL NEW DRUG EPOGEN MAY BE A GUIDE, BUT IT ALSO MAY PROVE TO BE AN EXCEPTION. THE HEALTH CARE FINANCING ADMINISTRATION (HCFA) HAS AGREED TO A SIX MONTH DEMONSTRATION GUARANTEEING A NEGOTIATED PRICE FOR THE DRUG WHEN ADMINISTERED IN KIDNEY DIALYSIS. THIS IS AN ESTABLISHED MEDICARE-COVERED PROCEDURE, A CAPTIVE MARKET, IF YOU WILL, IN WHICH IT IS RELATIVELY SIMPLE TO IDENTIFY COSTS.

WHAT REMAINS TO BE SEEN, HOWEVER, IS HOW THESE MARKETPLACE PRINCIPLES CAN BE APPLIED FOR THE AVERAGE MEDICARE BENEFICIARY PURCHASING VARIETIES OF PRESCRIPTIONS FOR THE ENTIRE RANGE OF MEDICAL CONDITIONS. I AM HOPEFUL THAT THIS MORNING'S HEARING WILL SET US ON THE ROAD TO PROVIDING FOR MEDICARE BENEFICIARIES THE BEST DEAL WE CAN IN SECURING AFFORDABLE PRICING FOR PRESCRIPTION DRUGS.

MR. CHAIRMAN, THANK YOU AGAIN, AND I LOOK FOWARD TO PARTICIPATING IN WHAT WILL SURELY PROVE TO BE A VALUABLE INFORMATION GATHERING PROCESS.

The **Chairman**. Senator Warner, thank you.

Senator Graham.

STATEMENT OF SENATOR BOB GRAHAM

Senator **Graham**. Thank you, Mr. Chairman. I wish to commend you for these very important hearings. I ask permission to submit an opening statement for the record.

Mr. Chairman, I would encourage this committee to look at the efforts which have been taken by a number of States. I see that we're going to have the State of Kansas represented today, where the effort has been made to use the ability of the State and large-scale purchases to the benefit of the older citizens of those States. I believe there are some important lessons there that can be applied at a national level.

Thank you, Mr. Chairman. I think this will be a very constructive series of hearings.

[The prepared statement of Senator Graham follows:]

BOB GRAHAM
FLORIDA

United States Senate
WASHINGTON, DC 20510

OPENING STATEMENT OF SENATOR BOB GRAHAM

UNITED STATES SENATE SPECIAL COMMITTEE ON AGING
Washington, D.C.
July 18, 1989
Hearing on Prescription Drug Pricing

I share Chairman Pryor's concern over the ever increasing cost of prescription drugs. As Senator from the State of Florida, representing three million elderly Floridians, I am pleased to participate in this hearing.

Health care costs, in general, have been continually rising for older Americans. On the average, they account for 16 percent of personal income, close to $1900 per year. For three out of four seniors in our nation, prescription drugs are the largest out-of-pocket expense they must pay.

Rising health care costs and an aging population create increasing pressures on public and private health care financing programs. While health care needs are increasing, the resources available to meet those needs are not. Because drug prices have been rising faster than economy-wide inflation since the 1970's, it is imperative that we study this component of health care costs.

I look forward to hearing from our panel of distinguished witnesses today. Their considerable expertise and testimony will help to us to better understand how prescription drugs are priced, and what role their pricing plays in overall health care costs.

The **Chairman**. Senator Graham, thank you very much for your statement.

Senator Kassebaum.

STATEMENT OF SENATOR NANCY LANDON KASSEBAUM

Senator **Kassebaum**. Thank you, Mr. Chairman. I'd like to ask that my full statement be made a part of the record.

You obviously can tell by the interest in this hearing that you've touched a very sensitive nerve, and I think it's a very important and timely hearing. I would just like to say, Mr. Chairman, briefly, that I have a rather parochial interest in this hearing. Although you have many fine witnesses testifying this morning, I'm particularly proud of one from Kansas, Winston Barton, the head of our State's SRS program. He is accompanied by John Alquest, the Commissioner of Income Maintenance and Medical Services at Kansas SRS.

It is an innovative program that we have in Kansas that he will be speaking about. It has attracted a lot of attention and I am sure it will be of great interest to the committee. It's a great pleasure to have Mr. Barton testifying here this morning.

[The prepared statement of Senator Kassebaum follows:]

Prescription Drug Prices
Special Committee on Aging
U.S. Senate
Senator Nancy Landon Kassebaum
July 18, 1989

- I would like to thank Chairman Pryor for calling this very timely and important hearing on the alarming rise of prescription drug prices.

- Prescription drug prices in this country are projected to jump about 9 percent in 1989. By comparision, the overall consumer price index is expected to rise only about 5 or 6 percent. Such rapid growth in drug prices has been going on for several years now, and shows only nominal signs of slowing down.

- As the implementation date for Medicare's new prescription drug benefit looms ever closer, it is imperative that we focus on the reasons for these price increases and begin examining ways to control them.

- Beginning in 1991, the Medicare program will be obligated to pay a significant portion of the drug costs incurred by the nation's elderly. As we are all aware, this benefit is rapidly shaping up to be much more expensive than anyone ever anticipated. Just last week, for example, the Congressional Budget Office released a report predicting a $4.7 billion shortfall in the catastrophic drug benefit by 1993. Clearly, the problem of rising prescription drug costs is one we can ill afford to ignore.

- I certainly appreciate the fact that pharmaceutical manufacturers must invest heavily in costly research in order to continue producing new and better drugs. Such medical innovation is vital to the nation's health --and it seems to me entirely reasonable that drug companies be allowed to pass at least some of this cost on to consumers.

- Nevertheless, there are those who seriously question whether the current rate of price increases can be fully explained by increased expenditures on research and development. Some would even go so far as to suggest that the free market is not working in the drug industry today. These are serious questions, and I am hopeful that the witnesses here today can help this committee arrive at some valid answers.

- We will hear today from a number of panelists well qualified to address the issue of rising drug prices. One of these, I am pleased to say, is Winston Barton, secretary of Social and Rehabilitation Services in my home state of Kansas.

- In his two years as secretary, Mr. Barton has nurtured the development of an innovative procedure for controlling drug expenditures in the Kansas Medicaid program. Using a system of soliciting bids from drug manufacturers, Medicaid in Kansas has begun to save significant sums of taxpayers' money. Although it is still in its infancy, the Kansas Medicaid "bid" program appears to hold significant promise, not only for my state, but for the nation as well.

- I commend Mr. Barton for his pathbreaking work, and I look forward to his testimony, as well as that of the other witnesses. Thank you.

The **Chairman**. Thank you, Senator Kassebaum.

I believe Senator Simpson is next.

STATEMENT OF SENATOR ALAN SIMPSON

Senator **Simpson**. Well, Mr. Chairman, what have you been up to? I mean, I just was gone for a few weeks——

The **Chairman**. I think this is the largest crowd of Senators that we've ever had at an Aging hearing. Thank you.

Senator **Simpson**. Did you count the cameras?

The **Chairman**. I have not counted them. [Laughter.]

Senator **Simpson**. It's important. Seven camera hearings are pretty good. But I think you've done well.

Well, my friend, you're embarked on one now, and Senator Pryor and I came to this remarkable place at the same time, the same year, and I have the deepest respect for him. I admire what he tries to do in this committee.

I will ask, Mr. Chairman, that the full text of my remarks appear in the record as if read in full.

We certainly have a vexing issue here in front of us. Catastrophic Health Care. We went through the anguish of crafting that bill; we heard the figures. You know, not everyone over 60 is in dire poverty in the United States. And I do get so tired of listening to so many special interest groups somehow trying to impel us along the road that everybody over 60 is in poverty, and just barely scratching through in this terrible society. That's not true.

There are people who are in poverty, but we spend a lot of time trying to find them to help them, or else we wouldn't have a budget of $1.2 trillion and a vote on a debt limit extension next month of $3.2 trillion. Now, that's what the debt limit extension of the United States is, and we'll vote on it next month, and it's $3.2 trillion. We are a pretty generous country. Unfortunately, we have people who don't always play the game like others should.

I don't know what we'll find here, Mr. Chairman, but the drug benefit is an important part of Catastrophic, and we're going to review that. These great divergences in price are rather stunning to me. I chaired the Veterans' Affairs Committee. I just don't know how you can take the same pill and peddle it at eight different price levels, and how that's right. And I really am interested in the difference between R&D and revenue, and profit, and I think it would be well worth investigating to see what we will come up with. And if we find that, as we crafted it, the Catastrophic Act assures that Government will pay top premium dollar, I'm going to be totally offended by that if that's the gimmickry that goes on, and these are the same guys that come shrieking around and hanging around our office like poor relatives asking about the deficit. [Laughter.]

They are in it up to their ham hocks if that's the case. I think I want to be right in the middle, helping to see what we can do with that.

And I thank you, Mr. Chairman.

[The prepared statement of Senator Simpson follows:]

Prepared statement of Senator Simpson

Thank you, Chairman Pryor, for calling this important and timely hearing on prescription drug prices and purchasing arrangements.

The new coverage of prescription drugs enacted under the Catastrophic Coverage Act is an important addition to the Medicare benefit package. However, CBO's recent cost estimates of the drug benefit suggest that, using the reimbursement formula spelled out in the law, we will have great difficulty supporting that benefit with scheduled revenues. Under the existing reimbursement formula, in fact, the program will run a deficit of nearly $3 billion by 1992.

Mr. Chairman, the drug benefit is important -- some argue that it is the most important -- protection for senior citizens contained in the new Catastrophic law. However, some are already arguing for repeal of this benefit based on deficit projections for the program. Before we take such drastic action, Mr. Chairman, perhaps we should reexamine whether our reimbursement mechanism assures efficient purchases on behalf of beneficiaries and guarantees maximum value for the dollar.

The federal government, by its sheer size, has awesome purchasing power and thus ought to be able to negotiate some of the best prices in the market -- without resorting to some sort of regulatory price fixing scheme. However, recent investigations by this Committee, HHS, and other Congressional committees suggest that we may have crafted a Medicare payment policy for prescription drugs that virtually assures that Medicare will pay top dollar for pharmaceuticals.

In addition, while crafting the Catastrophic Act, the Committees paid little attention to the relative value of the thousands of drug products for which Medicare will pay under this new law. Mr. Chairman, that is not wise policy. If this Committee's inquiry reveals that we have crafted a policy that has the federal government paying exhorbitant prices for pharmaceuticals of questionable value, then we should revisit that policy.

Thank you, Mr. Chairman. I look forward to hearing from our witnesses.

The CHAIRMAN. Thank you, Senator Simpson.

Our first panel is here today. I'm going to limit each witness to 3 minutes.

Well, let me first tell you folks about our first panel. Our first panel consists of persons who can get, or at least try to get reduced prices not only, Senator Simpson, for the Government, but also for the consumer. Our first witness is Dennis Styrsky, Chief of Pharmaceutical Products Division at the Department of Veterans Affairs, who will discuss what price discounts are at the Veterans Administration. We salute you, by the way, Mr. Styrsky, at being able to receive them.

Next will be Winston Barton, Secretary of the Kansas Department of Social and Rehabilitation Services, who will describe his State's innovative Medicaid bidding program, unlike any other in the country, and also the mixed success that he has had in obtaining reduced pricing from the drug manufacturers.

The final member is William Mincy, a partner in the Lenco Group consulting firm, who will describe how well the retail pharmacy buying groups have fared in securing discounts from the drug manufacturers.

The full body of your statements will be placed in the record, as will all opening statements of our members of the Aging Committee this morning.

Mr. Styrsky, you see the little green light. That means you're on. That's your warning, and then I'm going to have to cut you off in 5 minutes.

STATEMENT OF DENNIS STYRSKY, CHIEF, PHARMACEUTICAL PRODUCTS DIVISION, MARKETING CENTER, DEPARTMENT OF VETERANS AFFAIRS, HINES, IL

Mr. STYRSKY. Mr. Chairman and members of the committee, I am pleased to be here today to discuss the issues related to prescription drug pricing and the Department of Veterans Affairs' procurement program for prescription drugs.

Our mission is to provide drugs by the most economic method of supply to the Government customer by either contracting for depot stock or Federal supply schedule. In contracting for our depot stocked single source pharmaceutical products, discounts vary from 22 to 90 percent when compared to the average wholesale price, the variance being based on the manufacturers' pricing policies and willingness to negotiate for a market they possess. For multiple source drugs we typically obtain discounts ranging from 39 to 93 percent.

We have analyzed the cost of drugs from 1981 to the present for items in our depot distribution system. It is difficult to identify a trend in the cost because variables such as competition have a dramatic effect. It is relatively safe to identify single source drug costs as increasing annually.

We believe the contracting efforts by the Department of Veterans Affairs support efficiency and effectiveness in our program, since we have contained overall drug costs within or below the total marketplace. The effect of competition for multiple source drugs is evident through cost reduction. Multiple source drug prices have declined in our depot system an average of 51.7 percent below those prices paid in 1981 for the comparable brand name item.

In preparation for single source drug negotiations we obtain as much information as possible concerning the current pricing of the drugs for which we are contracting. This is accomplished by reviewing commercial publications such as the Drug Topics Redbook and a monthly publication which provides updates on brand name prices from Medispan. We also review the current Producer Price Index and prior year pricing as a minimum to prepare ourselves for negotiation. Generic drugs are reviewed the same way, but there is no question that the existence of competition is the driving force in negotiating the best prices for generics. Market awareness and price analysis confirm the reasonableness of the contract award, but if the offerors were not in direct price competition, the Department of Veterans Affairs would be in a less advantageous position.

Recently the Waxman-Hatch Act has had a positive influence in stimulating the introduction of generic drugs and the effect is very noticeable. Competition and large volume are the keys to favorable prices. Our negotiations are always carried out with the best interest of the Government in mind while recognizing the need for a win/win end result.

The Department of Veterans Affairs negotiates and manages its Federal supply schedules for drugs and pharmaceuticals under the format prescribed by the General Services Administration. Obtaining a Federal supply schedule contract for a proprietary product line on a multiple award schedule requires the disclosure of discounting practices for all classes of trade. Bidders complete a discount schedule and marketing data section of the solicitation with this information. We have developed a computer program which performs a price analysis of the drugs and compares the Government's position to the most favored customer supplied by the offeror. It also determines a negotiation objective for Government based on the analysis and prices offered other customers. The use of this program has enhanced our ability to negotiate under the Federal supply schedule and obtain better pricing for the Federal customer.

Our generic drug Federal supply schedule identifies the specific items we intend to have under contract. Offerors provide a price only. Since no disclosure data exists, we determine an average commercial price from all suppliers identified through the Redbook. This represents the maximum price determined reasonable for Government, and negotiations are conducted with suppliers to obtain an equal to or better price. If this is attained, the item is awardable. If not, no award is made to that supplier.

Our Federal supply schedule assignments are of the multiple award type because there are subtle differences even in therapeutic equivalent drugs. Buffering agents and tablet compression can be variables that are not addressed by the compendia.

Generally the Department of Veterans Affairs obtains discounts through its Federal supply schedule program averaging 41 percent for single source prescription drugs and 67 percent for multiple source drugs when measured against wholesale prices. We wish to emphasize that these prices represent the cost to the Government through commercial distribution channels and not drugs owned and distributed through depot stock.

Up to this point I have emphasized the positive factors in the Department's drug acquisition program; however, we do have to contend with certain adversity such as manufacturers that choose not to participate in either the Federal supply schedule or our depot distribution program. We meet these circumstances by seeking alternative sources that may be manufacturing the products which the Department requires. Success is unfortunately very limited.

The single problem encountered in negotiating with manufacturers generally relates to the market share Department of Veterans Affairs Medical Centers represent.

The **Chairman**. Mr. Styrsky, I apologize. I'm going to have to—our red light is on. We do have some questions and the full body of your statement will be placed in the record. I really appreciate your testimony, and we salute the VA for this very, very good buying program.

[The prepared statement of Mr. Styrsky follows:] [3]

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[3] See appendix 2, p. 348 for further information and answers to questions by the Department of Veterans Affairs.

STATEMENT OF

DENNIS M. STYRSKY

CHIEF, PHARMACEUTICAL PRODUCTS DIVISION

MARKETING CENTER

DEPARTMENT OF VETERANS AFFAIRS

BEFORE THE

SPECIAL COMMITTEE ON AGING

UNITED STATES SENATE

JULY 13, 1989

Mr. Chairman and Members of the Committee:

I am pleased to be here today to discuss the issues related to prescription drug pricing and the Department of Veterans Affairs procurement program for prescription drugs.

The Department of Veterans Affairs contracts and obtains drugs for its depot distribution program in support of the Medical Center network and other Government ordering offices. Also the Department has been delegated the Federal Supply Schedule responsibility for drugs and pharmaceuticals. We accomplish this by cost effective use of two multiple award Federal Supply Schedules, a commercial style catalog which is primarily for proprietary product lines and a Schedule of known generics with substantial use potential. This organizational structure provides total commodity management and a full overview of the Federal drug marketplace.

Our mission is to provide drugs by the most economic method of supply to the Government customer by either contracting for depot stock or Federal Supply Schedule. In contracting for our depot stocked single source pharmaceutical products, discounts vary from 22% to 90% when compared with the average wholesale price, the variance being based on the manufacturers' pricing policies and willingness to negotiate for a market they possess. For multiple source drugs we typically obtain discounts ranging from 39% to 93%, but most multiple source drugs in our depots are currently being purchased with discounts of greater than 80% from Average Wholesale Price. We have analyzed the cost of drugs from 1981 to the present for items in our depot distribution system. It is difficult to identify a trend in cost because variables such as competition have a dramatic effect. It is relatively safe to identify single source drug costs as increasing annually.

The VA and the Department of Defense have been actively involved in Shared Procurement for drugs and medical supplies since 1978. The Departments consolidate their requirements and assign contracting responsibility to one subordinate office, either the VA Marketing Center or Defense Personnel Support Center, Directorate of Medical Materiel. The program has been effective in maintaining reasonable prices for drugs. The Public Health Service was added to the agreement in 1984 and has been a user of the contracts negotiated by VA and DoD. Public Health Service has become actively involved in contracting through the vaccine acquisitions for childhood immunization. The Public Health Service's role is being expanded and soon they will absorb a greater portion of the contracting responsibility for drugs previously done by VA and DoD.

We would like to address three drugs on the committee's list. Atenolol, 50 mg, 100's, Dilitiazem Tabs, 60 mg, 100's, and Digoxin Tabs, .25 mg, 1000's are single source drugs that have been in the Department's depot distribution system for different periods of time. We have contracted for Atenolol since 1985, and it is currently costing the Department of Veterans Affairs 34% more than it did in 1985. Dilitiazem Tabs has been in the depot system since 1983, and the price has increased a total of 28% over the six year period. Digoxin has increased 656% since 1981 as a directed source procurement for the brand name Lanoxin but is still 22% below the Average Wholesale Price. These drugs overall are well within and below the Producer Price Index for prescription drug products which has increased an average of 9.5-13% annually for the past 10 years.

We believe the drastic increase in the price of Digoxin is related to the exceptionally low price that existed during the early 1980's. Increased demand associated with an aging population necessitated price adjustments for profitability in a relatively short time. Digoxin is reviewed annually prior to contract award and the pricing offered VA is consistently the best price available.

We believe the contracting efforts by the Department of Veterans Affairs support efficiency and effectiveness in our program since we have contained overall costs within or below the total marketplace. The effect of competition for multiple source drugs is evident through cost reduction. Multiple source drug prices have declined in our depot system an average of 51.7% below those prices paid in 1981 for the comparable brand name item.

In preparation for single source drug negotiations, we obtain as much information as possible concerning the current pricing of the drugs for which we are contracting. This is accomplished by reviewing commercial publications such as the "Drug Topics Redbook" and a monthly publication which provides updates on brand name prices from "Medispan". We also review the current Producer Price Index and prior year pricing as a minimum to prepare ourselves for negotiation. Generic drugs are reviewed the same way, but there is no question that the existence of competition is the driving force in negotiating the best prices for generics. Market awareness and price analysis confirm the reasonableness of the contract award, but, if the offerors were not in direct price competition, the Department of Veterans Affairs would be in a less advantageous position. The Waxman Hatch Act has had a positive influence in stimulating the introduction of generic drugs and the effect is very noticeable. Competition and large volume are the keys to favorable prices. Our negotiations are always carried out with the best interest of the Government in mind while recognizing the need for a "win/win" end result.

The Department of Veterans Affairs negotiates and manages its Federal Supply Schedules for Drugs and Pharmaceuticals under the format prescribed by the General Services Administration. Obtaining a Federal Supply Schedule contract for a proprietary product line on a multiple award schedule requires the disclosure of discounting practices for all classes of trade. Bidders complete a Discount Schedule and Marketing Data section of the solicitation with this information. We have developed a computer program which performs a price analysis of the drugs and compares the Government's position to the "most favored customer" supplied by the offeror. It also determines a negotiation objective for Government based on the analysis and prices offered other customers. The use of this program has enhanced our ability to negotiate under the Federal Supply Schedule and obtain better pricing for the Federal customer.

Our generic drug Federal Supply Schedule identifies the specific items we intend to have under contract. Offerors provide a price only. Since no disclosure data exists, we determine an average commercial price from all suppliers identified through the "Redbook". This represents the maximum price determined reasonable for Government, and negotiations are conducted with suppliers to obtain an equal to or better price. If this is attained, the item is awardable. If not, no award is made to that supplier. Our Federal Supply Schedule assignments are of the multiple award type because there are subtle differences even in therapeutic equivalent drugs. Buffering agents and tablet compression can be variables that are not addressed by the compendia.

To substantially strengthen the Government's ability to obtain lower prices, we have required all manufacturers and distributors interested in contracting under the proprietary Federal Supply Schedule program to provide their actual commercial sales data to the Government for any item they propose to include in their contract. Items with less than $2,000 in annual sales to Government will not be considered for award, nor will a contractor who cannot provide more than $25,000 annually in total Government sales. The significance of these thresholds relates to the need for the specific item. The annual sales must exceed the Small Purchase Authority prescribed in the Federal Acquisition Regulations. Failing in either of these categories makes the cost to negotiate, award and administer a contract unfavorable for the Department of Veterans Affairs since any Federal ordering office could make a single purchase under the Small Purchase Authority for the entire Government. Conversely, we identify those products for which the Government makes substantial purchases, and we negotiate on the strength of this volume.

Generally the Department of Veterans Affairs obtains discounts through its Federal Supply Schedule program averaging 41% for single source prescription drugs and 67% for multiple source drugs when measured against wholesale prices. We wish to emphasize that these prices represent the cost to the Government through commercial distribution channels and not drugs owned and distributed through depot stock.

We are reducing the cost to contract with the Government by eliminating duplication of contracting within the Department of Veterans Affairs. Our goal is to make our organization more effective by bringing basic business principles and procedures into Government contracting. Use of Federal Supply Schedule requote and tiered pricing procedures established by the General Services Administration has given us the ability to reduce the costs associated with doing business with Government. This has established the significance of the Federal Supply Schedule contract, and, through this and traditional contracting methods, we maintain total support for the Department of Veterans Affairs and all other Executive Branch Federal activities.

The benefits of the requote/tiered pricing procedures are:

1\.

Establishes through Multiple Award Federal Supply Schedule the broadest competitive base from which single award contracts can be awarded.

2.
Accomplishes all special program functions more economically and efficiently such as adding items in support of central distribution.

3.
Presents a single face to industry of total Government requirements through a uniform method of contracting with one primary Government contracting activity.

4.
Reduces duplication of effort and resources by Government and Industry to provide pharmaceuticals for various delivery systems.

5.
Maximizes Government leverage in negotiations and provides the needed flexibility to react and acquire generic equivalents when they enter the marketplace resulting in quick response to changing market conditions and lower cost.

Up to this point, I have emphasized the positive factors in the Department's drug acquisition program; however, we do have to contend with certain adversity such as manufacturers that choose not to participate in either the Federal Supply Schedule or our depot distribution program. We meet these circumstances by seeking alternative sources that may be manufacturing the products which the Department requires. Success is unfortunately very limited.

The single problem encountered in negotiating with manufacturers generally relates to the market share Department of Veterans Affairs Medical Centers represent. A decade ago, VA was 1 of the 5 largest customers to the pharmaceutical industry. Today, due to the consortia, buying groups and Health Maintenance Organizations, it is not even among the 10 largest buying organizations in the United States for drugs and pharmaceutical products. We believe the the closed system of drug acquisition by the Department of Veterans Affairs in its business dealings assist us in overcoming the this obstacle when negotiating our prices.

For the convenience of the committee, the responses to the six questions forwarded by the staff are attached.

I appreciate the opportunity to provide this information to the committee.

The **Chairman**. Mr. Winston Barton, Secretary of the Kansas Department of Social and Rehabilitation.

Mr. Barton.

STATEMENT OF WINSTON BARTON, SECRETARY AND CHIEF EXECUTIVE OFFICER, KANSAS DEPARTMENT OF SOCIAL AND REHABILITATION SERVICES, ACCOMPANIED BY JOHN ALQUEST, COMMISSIONER, KANSAS MEDICAL PROGRAM

Mr. **Barton**. Thank you, Mr. Chairman, and members of the committee. I am Winston Barton, Secretary of the Kansas Department of Social and Rehabilitation Services. With me is John Alquest, our Commissioner of Income Maintenance and Medical Services. SRS is an umbrella agency responsible for public social services, which includes the Medicaid Program in Kansas.

The primary reason I am here today is that I believe we all have an obligation to consider ways to contain or reduce expenditures in the Medicaid prescription drug program. We must address the rate of inflation in the cost of drug products and the need to provide a balanced health care program for the needy within the limits of State and national resources. Available funding for health care services is not unlimited.

The major area of the program I want to report to you this morning relates to our efforts in establishing bidding procedures which we feel are unique. You have a copy of our report that reveals details on the program. Therefore, I will not elaborate so much on how it works, but briefly describe some of the obstacles we have encountered in starting this initiative.

Our bid program is somewhat different than traditional bid programs in that the State does not buy directly from pharmaceutical manufacturers. The mechanism is, however, quite simple. First, we issue an invitation to bid; the bid winner is selected; a sole source contract is signed; the providers, the physicians and pharmacists, are notified of which products are covered, and told of the comparable products that are not covered; claims are submitted by the pharmacist to the State for each prescription dispensed utilizing the National Drug Code; the State Medicaid fiscal agent calculates the units and cost from the providers, that's the pharmacist who submits a claim to the State; the bid winner, the manufacturer, is invoiced for the difference between the accepted bid and the reimbursement amount from the claims submitted by the pharmacist; the bid winner, the manufacturer, reimburses the State on a monthly or quarterly basis the difference between the bid and the amount paid to the pharmacist by the State.

In this system, everyone participating wins. The pharmacist has purchased his supply from his usual source and is paid his usual cost. The recipient obtains his prescription without delay. SRS has reduced the final cost of the drug product. The bid winner can be assured of a steady volume of business during the term of the contract.

The major obstacle in starting the program was the strong resistance from the major pharmaceutical companies. The brand name companies have generally not been interested in bidding. In a recent discussion with a pharmaceutical representative it was suggested that his company should support a Medicaid bid program and become very competitive, not only in Kansas, but in all States. His reply was simply that his company was not interested. It was difficult to understand why a company would not be interested in a potential national bid contract that could exceed $200 million annually for one drug.

One reason pharmaceutical companies are not interested is that it will cut into their profits, especially if they lose the bid. As you know, most medical providers who serve Medicare and Medicaid recipients do not make a profit, and many lose money. For example, hospitals and nursing homes would probably go out of business if their total patient load were Medicaid and Medicare clients because Government payments frequently do not cover costs. Physicians in many States receive only about one-half their normal fees when they care for Medicaid recipients. Most pharmacists are fortunate to cover actual costs when they fill prescriptions for Medicaid recipients. I contend that pharmaceutical companies are the only entity in the health care field that do not pay their fair share in meeting the health care needs of the poor of this country.

Bidding of prescription drugs has a much greater cost savings potential than we have developed so far in Kansas. Our State expenditures in fiscal year 1989 will exceed $27 million for prescribed drugs for Medicaid recipients. Nationally, over $2.8 billion is spent annually by the Federal and State Governments for prescribed drugs for Medicaid recipients.

Our bid program in Kansas will only save a few hundred thousand dollars this year, primarily due to the lack of participation by the pharmaceutical companies. However, I believe there's a potential savings in Kansas of $2 million to $4 million annually. On a national level the savings to the State and Federal Governments could be in the hundreds of millions of dollars.

Kansas pays over $2 million a year for ulcer medicine that we refer to as H2 antagonists. If the State could receive a bid savings of 25 percent, which is very realistic, the State could save $500,000 on this one drug. Nationally, States pay over $200 million for the ulcer medicines for Medicaid recipients. A 25 percent savings would be $50 million. Expand that savings to other prescribed drugs, and it is not difficult to realize the potential savings.

I believe the Kansas bid program could be designed to fit the needs of most all State Medicaid programs and—of great concern to you and your committee, Mr. Chairman—it could be made to work in the Medicare Program.

Mr. Chairman, I have two recommendations on how your committee can help States develop their bid programs. One, encourage the Health Care Financing Administration to promulgate regulations that encourage States to implement bid programs. Two, through legislation provide a higher FFP for prescribed drugs to States that contain or reduce cost through bidding.

And finally, Mr. Chairman, I recommend you encourage HCFA to actively seek ways to incorporate a bidding procedure in the Medicare Program.

Thank you, Mr. Chairman.

[The prepared statement of Mr. Barton follows:]

State of Kansas
Department of Social and Rehabilitation Services
Winston Barton, Secretary

The Kansas Medicaid Prescription Drug Bid/Contract Process

The Kansas Medicaid bid/contract program for pharmaceuticals administered by the State Department of Social and Rehabilitation Services (SRS) is an innovative approach to cost containment for the Medicaid Prescription Drug Program. The bidding process, however, has been in use in other applications such as hospitals and buying cooperatives for many years.

This program is a combination of a standard invitation for bid and contract award along with the "chargeback" system used by buying groups. The difference between the Kansas Medicaid Bid/Contract Program and other bid programs is that the Medicaid Program does not take delivery of drugs. Cost concessions from drug manufacturers are based on claims submitted by Pharmacy Providers for specified products, which have been dispensed to Medicaid recipients from the pharmacies' regular inventory. The bid winning manufacturer is then invoiced by the Medicaid Program for the difference between the reimbursed inventory cost and the contracted price. This "adjustment" payment is returned to the Kansas Department of Social and Rehabilitation Services.

The rationale for development of a Medicaid Bid/Contract Program is that many state agencies and institutions providing health care services, and specifically pharmacy services, receive discounted pricing for drug products from pharmaceutical manufacturers in response to requests for bids. Reduced cost pharmaceutical contracts are also available to many other not-for-profit as well as for-profit health care organizations; but they, like the Kansas institutions, take possession of the drugs contracted. The question was how could the Medicaid Program receive the reduced cost benefit from these or separate bids without violating federal antitrust laws, such as the Robinson Patman statutes on discriminatory pricing?

The concept developed is a system that does not interfere with normal drug distribution channels nor pricing practices to pharmacies by manufacturers or drug wholesalers, and thus Robinson Patman is not violated. This concept does not alter the reimbursement system or the level of payments to pharmacy providers. The bid arrangement and cost adjustment is between the pharmaceutical manufacturers and SRS. This is a unique approach to containment of drug product costs which has not been implemented by any other Medicaid program. Projections of potential cost savings are significant, Attachment (1).

This program seeks to reduce costs at a logical point in the distribution channel. The provider pharmacies' dispensing fees have remained relatively flat, but the cost of the total program has doubled within a few years due to continuing price increases by pharmaceutical manufacturers. This is true even though recipient benefits have been reduced. Many drugs are now going off of patent, with a consequent reduction in cost of availability due to a competitive market, but the newly-marketed drugs are so expensive as to cause double-digit inflation in total prescription drug cost each year. If the extraordinary inflation of drug costs is to be controlled, it must be at the manufacturing level. The bid program reduces costs without sacrificing quality or hurting providers of pharmacy services. However, it has been met with much resistance from individual companies and special interest groups of the pharmaceutical industry.

Although a few brand name pharmaceutical companies have submitted bids, most have reacted negatively when asked to give the state social services agency the benefit of the lower costs charged to other public and private institutions. Individually and through their primary trade association, the Pharmaceutical Manufacturers Association (PMA), they have actively fought against the concept of bidding for Medicaid contracts even when they are competitively bidding for other government and private contracts. Lobbying of the state legislature concerning pharmaceuticals has been heavy in Kansas as well as in other states where some form of cost control of pharmaceuticals has been actively pursued.

While the above-described concept has been received with significant resistance from the brand name pharmaceutical manufacturing community, it is of interest that during the late 60s and early 70s a very similar type of arrangement was in effect with many of the major pharmaceutical manufacturers. During this time period, they provided to the agency a cost adjustment, percentage rebate, or participation payment (whatever term may be appropriate), based on the dollar volume of their products reimbursed to providers of pharmacy services for Medicaid prescriptions. One consideration provided to manufacturers for participation in the program was that their total product line would be included as covered services. This program was discontinued primarily due to the desire of manufacturers. A reason for their reluctance to continue participation at that time was pressure they felt from pharmacy practitioners concerning discriminatory pricing practices. However, other multi-tier pricing structures by pharmaceutical manufacturers are still common. Recent information on pricing indicated some companies currently have eight different classes or tiers: retailers, wholesalers, chain wholesalers, mail order, nursing homes, Health Maintenance Organizations (HMO), hospitals and physicians. Although not necessarily ranked in the order listed, retailers invariably will have legal access only to the highest levels of wholesale prices.

The multisource (generic) pharmaceutical manufacturers, individually and through the Generic Pharmaceutical Industry Association (GPIA), have not to our knowledge actively lobbied against our bid program. In fact, they seem to recognize the realities of this competitive opportunity. They clearly understand their disadvantage in programs where the prescriber can override maximum cost limits.

One of the most controversial, but certainly one of the most cost-effective, facets of the Kansas bid program is competitive bidding of therapeutic alternate products. First, I must explain that this program does not require or imply that the pharmacist substitute drugs that are not generically equivalent. In other words, therapeutic substitution by the pharmacist is not involved. However, the pharmacist will, on occasions when the prescriber orders a drug not covered due to the bid program, contact the prescriber and suggest that a new order for the covered product be issued.

Therapeutic alternates are drugs that are neither generically nor therapeutically (by FDA standards) equivalent. Therapeutic alternates are different drug entities that are used to obtain the same results. For example, none of the Histamine-Two Antagonist (H_2A) drugs that are currently available for treatment of ulcers are generic or therapeutic equivalents. However, unbiased experts indicate that they can all be used to obtain the same results. The Kansas Medicaid Program did not receive an acceptable bid from the H_2A

manufacturers, so the manufacturer with the lowest price on these therapeutic alternates was selected to be the sole source provider for one year.

Another therapeutic alternate class did have an acceptable bid. The multiple brand and generic products of sustained-release potassium chloride that are available make it a highly competitive field in which to market a new - or old - product. A new brand from a reputable manufacturer was accepted on the bid/contract program. In sustained-release form, most of the potassium products are neither generically or therapeutically equivalent. They are, however, therapeutic alternative products for potassium supplementation. This brand has more recently been declared by the FDA to be therapeutically equivalent to the reference product.

In addition to therapeutic alternates, bids are invited for generically equivalent products. Generic equivalent drugs can be further divided into multisource products for which the patent has expired, and licensed duplicate drugs. Duplicate drugs are generically equivalent drugs sold under more than one brand name, and marketed by different subsidiaries of the patent holder, or by different companies under license from the patent holder.

When a sole-source contract is in effect, only the specific National Drug Code (NDC) numbered products contracted for are covered. Other products, whether they are generically or therapeutically equivalent, or are therapeutic alternates, are noncovered as specified in the contract. To rephrase my earlier statement, the pharmacist is not authorized to change a prescriber's order, even when it is for a product noncovered due to the bid program. The pharmacist may, however, contact the prescriber to obtain a new prescription for the covered product, so that it can be dispensed and billed under the Medicaid Prescription Drug Program.

The original group of drugs for which bids were invited in 1987 was selected to represent several therapeutic classes, and different marketing categories (prescription required or no prescription required), as well as therapeutic alternate drugs, and, of course, generically equivalent drugs, from both multisource manufacturers and licensed duplicate drugs.

Not all drugs, either branded or multisource, will have therapeutic alternates available. The list of "biddable" drugs is not infinite, but it can be expanded over the list used each of the past two years.

The Kansas Medicaid Prescription Drug Bid Program has delayed its bid invitation for 1989-1990 because of interest expressed by several states in joining in a possible multistate bid program. We have developed a questionnaire for distribution to determine if enough interest exists to undertake such a concept on a multistate basis. Kansas Attorney General Opinion #89-74, Attachment (2), concerning such a multistate program has been received, and we will proceed to determine the commitment of other states to this concept.

A letter, Attachment (3), is enclosed, with information similar to that sent to other states who have requested data about the Kansas Bid Program. I have also enclosed, Attachment (4), the invitation for bid letter from March, 1988 which gives the full details of the contract. Item 10 on Page 3 of the Special Conditions section defines the key provision of Adjustments to Contract Payment.

The obvious incentive for a manufacturer to bid is that the agency will include as covered pharmacy program services only those products with a successful bid. The bid winner becomes the sole-source provider for the term of the contract. This, of course, translates into a significant increase in the bid winner's sales.

The Kansas program is two years old, and covers only a half-dozen products. Bidding has the potential to produce much greater savings to the Medicaid Program than has currently been demonstrated.

Federal Upper Limits (FUL) on Drug Reimbursement

The aggregate upper limits of payment for drugs as specified by HHS, HCFA, in 42 CFR, 447.331 and 332, refers to both multiple-source drugs specifically listed, and "other drugs", which include those multiple-source drugs not specifically listed and other-than-multiple-source drugs. "Other Drugs" are limited in reimbursement to the Estimated Acquisition Cost (EAC). Since definitions of EAC vary from state to state, reimbursement levels for "other drugs" may not be consistent between the states.

An enclosed copy of HHS Secretary Sullivan's recent letter to Charles West of the National Association of Retail Druggists (NARD), Attachment (5), indicates that an unmodified Average Wholesale Price (AWP) will not be acceptable as the Estimated Acquisition Cost (EAC). Despite the very active opposition by pharmacies and their organizations, we feel that most pharmacists will accept the decision to reimburse at an Estimated Actual Acquisition Cost (EAAC) if an adequate dispensing fee, based on actual costs, is funded.

The federal government and many states developed Maximum Allowable Costs (MAC) several years back. The federal MAC was not expanded until the new Federal Upper Limits (FUL) was implemented in October 1987. Many states, however, took the lead in broadening the scope of pharmaceutical cost control using State Maximum Allowable Costs (SMAC). Some SMACs are little different from Average Wholesale Price (AWP), and few are as low as the FUL, but many states also SMAC a broader list of drugs than required by the FUL regulations. States have implemented many other cost-containment measures, also. Kansas has taken the lead in implementing a Medicaid Bidding Program as a cost reduction program.

The portion of this regulation which concerns those multiple-source drugs specifically listed under Section 447.332 is certainly the subject of many criticisms by provider pharmacies, their suppliers and Medicaid programs. Generally, the criticisms are towards the mechanisms, more than the philosophy of setting "ceiling" prices, however. There are, of course, many prescribers and recipients who resent having their prerogatives restricted in any manner. There are pharmacies, likewise, which resent the restrictions and the extra work that inevitably goes with any restriction. There are also those partisans of the brand name manufacturers who do not believe the FDA ratings on therapeutic equivalency of generically equivalent drugs. In today's marketplace these types of objections usually result from some form of self-interest or refusal to accept reality. The need for reasonable and consistent cost control is clearly evident.

There are many objections voiced to the mechanisms of implementation of cost limits for drugs listed pursuant to Section 447.332 that do need more consideration. Listed below, not necessarily in order of importance, are several problems generated by the Federal Upper Limits (FUL).

Availability to the pharmacy provider of the listed drug at or below the listed cost. The federal formula of 150% over the lowest cost found anywhere nationally sounds generous, and may be in a highly competitive wholesale market area such as Baltimore. Such availability is not consistent nationally. Many pharmacists from rural states have complained about lack of availability at appropriate prices in their region. For those pharmacists who can buy their products at the lower prices available, a potential 50% markup on cost is extra gross profit that the less fortunate pharmacies will not receive.

The aggregate features of reimbursement audits make it essential to have sophisticated computerized capability to track the 400 drug entities currently listed (usually with multiple NDCs). If one drug is not available at the Federal Upper Limit (FUL), or for other reasons the FUL is not implemented, other drug prices can be cut below the FUL. However it is not just a simple exchange. The volume of each drug's use and the respective variances above and below the FUL must balance out at payments no greater in aggregate than if all were reimbursed at the listed price. Simply stated, it is complicated to implement any variance, no matter how important such a variance might be. For our system, we found it necessary to purchase a previously unneeded pricing service, and make extensive computer programming additions. It still takes too long to calculate the effect any variation in pricing will have or to implement new price lists during the unreasonably short time allowed before the implementation date. The pharmacies must, of course, be notified of the new prices on a timely basis, also.

Another factor is updating costs based on market conditions as they change. When the lowest available cost increases coincidentally with, or shortly after a new price list is published, the pharmacy may be either reimbursed at less than his cost - or more likely - will refuse to dispense, and the recipient is denied a benefit.

Some states have statutes that prevent the pharmacist from dispensing generically for certain drug classes, such as the Schedule II narcotics. Also many individual pharmacies, as well as both prescribers and their patients, object to the principle of "brand exchange" for specific products, as may be necessary to stay within the cost limitations. While this feeling is exceptionally strong for anticonvulsants and oral contraceptives, it also occurs with almost any multisource drug. Much of this involves emotional feelings, rather than factual considerations. It is, however, a frequently heard argument that will probably continue as long as ceiling costs continue.

Kansas Medicaid Prescription Drug Cost Reduction Program

SUMMARY

There are many forms of cost controls that can be, and have been, implemented. This testimony centers on reduction of costs through bid contracts and ceiling costs as implemented both at the state and federal levels.

The bid program promotes competition, and does not eliminate the possibility of brand name drug versions of generically available products being the low bid. Invariably a cost ceiling such a SMAC or FUL will eliminate the brand names on the basis of published cost. The Pharmaceutical Manufacturers Association (PMA) and their brand name manufacturer members have not acknowledged this bidding system as a competitive opportunity.

The formulas for selecting and pricing drugs for the multisource list creates numerous inequities between (1) drug products listed and those similar products not listed and (2) in availability within cost limitations in different geographic regions.

ATTACHMENT (1)

Bid Adjustments Received and Projected

Projected Fiscal Impact of Medicaid Bid Program based on the one year, eleven months history of "Adjustments" received as of May 30, 1989.

Fiscal Year	Products On Bid Call	Products Contracted	Adjustment Dollars Received	Projected Adjustment Dollars	Average Savings Per Product
1987	20	1	$ 1,255	----	----
1988	20	1	52,688	----	----
87/88	20	1	53,943	----	$53,943
1989 11 mos.	20	6	$145,172	$158,369	$26,395
1990	150 projected	30 projected	----	$791,850	$26,395

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1988-1989 BID CONTRACT DRUGS

Drug Class (& Usage)	Representative Brand Name	Generic Name	Brand Average Wholesale Price	Representative Generic Average Wholesale Price	Bid/ Contract Net Price
Antibiotic for infections	Keflex	Cephalexin 250 mg	$0.7646 cap	$0.4785	$0.2095
Antibiotic	Keflex	Cephalexin 500 mg	1.5026 cap	0.9209	0.4075
Diuretic for blood pressure	Dyazide	Triamterene/ HCTZ 50/25	0.5657 cap	0.3863	0.2688
Diuretic	Maxzide	Triamterene/ HCTZ 75/50	0.4095 tab	0.2790	0.2000
Diuretic	Zaroloxyn	Metolozone 5 mg	0.2321 tab	No generic	0.1198 tab
Antacid for ulcers, etc.	Amphojel	Aluminum Hydroxide	0.0099 ml	0.0082 ml	0.0051 ml
Potassium Supplement for use with some diuretics	Micro-K	Potassium Chloride Sustained Release/10mEq	0.0905 cap/tab	0.0713 cap/tab	0.0425 tab
Bronchodilator for breathing problems	Theolair	Theophylline 80mg/15ml	0.0265 ml	0.0068 ml	0.0040 ml

A commonly prescribed representative brand name is shown followed by the generic name of the drug entity, with the dosage form and dose. The three cost columns list the then current brand cost and a representative generic company's cost, both at Average Wholesale Price (AWP) and the final net cost to the state under the actual contract.

Notes: The cost figures are by dosage unit (tablet or capsule) for the oral solids, and by milliliter volume (ml) for the liquids. Some brand and generic prices have changed since these contracts were signed, but the bid price remained constant. There are no generics of metolozone, but there are two brand names of the product marketed by different companies.

EES:csl
06/26/89

ATTACHMENT (2)

KANSAS SOCIAL AND
REHABILITATION SERVICES

JUN 5 1989

OFFICE OF THE
SECRETARY

STATE OF KANSAS

OFFICE OF THE ATTORNEY GENERAL

2ND FLOOR KANSAS JUDICIAL CENTER, TOPEKA 66612-1597

ROBERT T. STEPHAN
ATTORNEY GENERAL

MAIN PHONE (913) 296-2215
CONSUMER PROTECTION 296-3751
TELECOPIER 296-6296

June 14, 1989

ATTORNEY GENERAL OPINION NO. 89-74

Winston Barton, Secretary
Social and Rehabilitation Services
Docking State Office Bldg., 6th Floor
Topeka, Kansas 66612

RE: Commerce and Trade -- Monopolies and Combinations in Restraint of Trade -- Discrimination in Price; Discrimination; State Drug Bidding Program; Participation by Other States

Monopolies and Unfair Trade -- Restraint of Trade; General Provisions -- Unfair Trade

Synopsis: Although the proposed drug bid program raises serious antitrust questions, it is our opinion that it does not represent a *per se* violation of antitrust laws. Under a rule of reason analysis the proposed bid program may survive an antitrust challenge. The proposed program should be conducted in a manner that renders the market more, rather than less, competitive and does not allow one manufacturer to unlawfully possess market power to the exclusion of its competitors. Cited herein: 15 U.S.C. § 1-27.

* * *

Dear Secretary Barton:

You request our opinion concerning a proposed pharmaceutical bid program and extension of that bid program to other states wishing to participate. You specifically ask whether the bid process and the extension of the process to other states violates antitrust laws.

Pursuant to conversations with and correspondence from the Department of Social and Rehabilitation Services (SRS) and its legal staff, we understand that the bid process works as follows: SRS solicits and accepts separate bids on each of certain specific drugs from any and all manufacturers of that drug; each drug is separately bid; bids will be accepted on the generic equivalent as well as the therapeutic version of each drug; the manufacturer who submits the winning bid on each drug will become the only manufacturer of that drug that SRS will reimburse (when that manufacturer's brand of the drug is used by Medicaid/ MediKan recipients); only one manufacturer for each type of drug will be so designated and SRS will not reimburse for brands of the same drug manufactured by unsuccessful bidders; when a participating provider-pharmacist dispenses the designated drug to a Medicaid/MediKan recipient, that Medicaid/MediKan recipient must pay a flat co-payment fee to the pharmacist; the provider-pharmacist then submits a claim to SRS; SRS reimburses the participating provider-pharmacist for the costs of the designated drug that the co-payment fee did not cover; SRS then takes all the claims it has received from participating provider-pharmacists and submits those claims and amounts to the bid winner for each drug; the winning drug manufacturer then gives a rebate to SRS for the difference between the amount SRS paid to the provider-pharmacist and the amount of the winning bid price.

For example: (1) the winning bid is accepted from a manufacturer at $1.00 per unit for drug Z; (2) drug Z is sold by the manufacturer to a participating provider-pharmacist for $2.50 per unit; (3) a Medicaid/MediKan recipient buys drug Z from that participating provider-pharmacist, who charges a retail price for the drug of $5.00 per unit; (4) the Medicaid/MediKan patient pays the required flat fee co-payment of .50 cents per unit; (5) the participating provider-pharmacist submits a claim for the unpaid cost of the drug, $4.50 or $2.00 (dependent upon whether SRS reimburses wholesale or retail costs); (6) SRS submits a claim to the winning manufacturer for the difference between the provider-pharmacist claim ($4.50 or $2.00) and the winning bid ($1.00), $3.50 or $1.00. The amount paid from the winning manufacturer to the state is characterized as a rebate. The rebate paid to SRS from the winning bid manufacturer will be paid to the state general fund.

SRS believes this bid program will result in cost containment for the state and has used this drug bid procedure for almost two years. Approximately 95% of all Kansas pharmacies participate in supplying drugs to Medicaid/MediKan recipients.

Certain unavailable information may have a significant impact upon the permissibility of the proposed bid program: details concerning geographic market; the relevant market share and market power; the intentions of the participating states or other entities; the exact nature of the interstate cooperation agreement; each participating state's enabling legislation; and the length of time the bid and the interstate agreement will be in effect. As we do not have specific information concerning these and other possible fact issues, this opinion is general in nature and is limited to a discussion of antitrust principles as they apply to the facts currently before us. It is hoped that the discussion contained herein will provide guidance and allow SRS to conduct the bid program procedure in accordance with and mindful of antitrust principles.

You state that the details and terms of a multi-state program have not been established. Because many states are interested in participating and because the successful bid winner's brand could become the only brand that states will reimburse Medicaid recipients for, the successful bid winner could significantly increase or assure itself of a large market for each drug. The geographic market, market share and relevant market for each successful bidder cannot be ascertained at this point. Nevertheless, it is obvious that should a significant number of states participate nonsuccessful bidders could potentially lose or be precluded from obtaining a significant amount of business. Nonsuccessful bidders would be able to sell their product to pharmacies wishing to stock their brands and pharmacists remain able to sell any brand of drug to the general public or to state and federal aid recipients, but any Medicaid recipient wishing to have the state pay drug costs will have to purchase the approved brand. Thus, pharmacists have a strong incentive to stock adequate quantities of that brand and Medicaid recipients are extremely likely to request that brand.

The general purpose of antitrust laws is the subject of much discussion between legal authority and economists. Broadly and generally stated, antitrust laws seek to promote, encourage and maintain competition and to prevent harmful monopolies. See generally City of Chanute, Kansas v. Williams Natural Gas Company, 678 F.Supp. 1517 (Kan. 1988); 54 Am.Jur.2d Monopolies § 1 (1971); 58 C.J.S. Monopolies § 15 (1948).

The Sherman Act, 15 U.S.C. §§ 1-7, forbids monopolizing trade in broad and general terms. Violation requires the possession of monopoly power in a relevant market and the knowing intentional acquisition of that power by two or more conspirators. McKenzie v. Mercy Hospital of Independence, Kansas, 854 F.2d 365, 367 (10th Cir. 1988). The Clayton Act, 15 U.S.C. §§ 12-27, prohibits specific anticompetitive behavior outside the broad scope of the Sherman Act. See generally 54 Am.Jur.2d Monopolies § 111 (1971). The Clayton Act seeks to promote competition through protection of viable, small and locally owned businesses. Ford Motor Company v. United States, 405 U.S. 562, 92 S.Ct. 1142, 31 L.Ed.2d 492 (1972). The Robinson-Patman Act was enacted to strengthen sections of the Clayton Act and seeks to protect small businesses unable to purchase in quantity. See FTC v. Morton Salt, 334 U.S. 37, 68 S.Ct. 822, 92 L.Ed. 1196 (1948). State antitrust laws vary in scope and application and each participating state must examine its own antitrust laws.

In order to determine whether a particular action violates antitrust laws it becomes necessary to characterize the questioned or challenged activity. Antitrust principles look at two types of anticompetitive relationships, horizontal and vertical. Horizontal restraints are arrangements between entities operating on the same level; manufacturers, suppliers or buyers. The proposed interstate drug bidding arrangement could be characterized as a horizontal arrangement between two entities operating on the same level, i.e. states as buyers or insurers. Practices that may result in a prohibited horizontal restraint include price fixing, boycotts of a product, manufacturer or customer, and mergers resulting in a monopoly. See Vakerics "Antitrust Basics", pp. 6-1 through 6-49 (1988). Vertical restraints are conditions or restrictions agreed to, imposed or directed at entities operating at different levels. Vertical relationships which may exist in the proposed drug bidding program include the relationship between the states and the drug manufacturers, the states and the provider-pharmacists, the states and the general public, and the states and the benefit recipients. Vertical restraints include dictating resale prices, Arizona v. Maricopa County Medical Society, 457 U.S. 332, 102 S.Ct. 2466, 73 L.Ed.2d 48 (1982), or non-price restraints such as territorial or customer restrictions, price discrimination, exclusive dealing or requirement contracts, and tie-ins. Antitrust restraints that may be implicated by the proposed bid program include price fixing, boycott, price discrimination, and requirement contract considerations.

Price fixing restraints are traditionally considered per se illegal, while non-price restraints are more often subject to the rule of reason. Courts currently evidence a reluctance to impose a per se rule unless there is clear evidence of intent to monopolize or otherwise hinder helpful competition. Rather, courts now frequently use a rule of reason analysis to determine antitrust violations. Under the "rule of reason" the legality of restraints on trade is determined by weighing all the factors in a case, such as the history of the restraint, the evil believed to exist, the reason for adopting the particular remedy and the purpose or ends thought to be attained. Blacks Law Dictionary 1196 (5th ed. 1979).

Generally, price fixing is any combination formed for the purpose and effect of raising, depressing, pegging, or stabilizing the price of a commodity. United States v. Socony Vacuum Oil Company, 310 U.S. 150, 223, 60 S.Ct. 811 84 L.Ed. 1129 (1940). Sharing information on prices may also result in improper price fixing. See United States v. Container Corporation of America, 393 U.S. 333, 89 S.Ct. 510, 21 L.Ed.2d 526 (1969). However, where third parties are not affected by the price fixing scheme, a rule of reason will usually be applied. Medical Arts Pharmacy v. Blue Cross and Blue Shield, 675 F.2d 502 (2d Cir. 1982). See generally Hjelmfelt, "Antitrust and Regulated Industries", pp. 42-45 (1985).

The proposed bid program does not appear to be a vertical or horizontal price fixing scheme. The states are a large buyer or buyers seeking the lowest price on a commodity. If the states were considered competitors there could be a possible horizontal price fixing charge against them. However, the proposed drug bid program does not dictate and will not automatically affect the price charged to and paid by participating provider-pharmacists to the drug manufacturer. Moreover, the resale price to the general public or benefit recipients is not dictated by the drug bidding program. The bid reflects the price at which each manufacturer independently agrees to ultimately provide the drugs to the state or states. The states ask that each manufacturer fix its own individual price, and the states remain free to either accept or reject each bid. Thus, the price is fixed by the manufacturer not by the states, and it is therefore unlikely that a price fixing claim would succeed.

Another possible antitrust principle that may be involved concerns boycotts. A boycott is "a method of pressuring a party . . . by withholding or enlisting others to withhold patronage or services." St. Paul Fire and Marine Insurance Company v. Barry, 438 U.S. 531, 541, 98 S.Ct. 2923, 57 L.Ed.2d 932 (1978). A boycott may be illegal if it impermissibly increases market strength through concerted efforts.

The Fifth Circuit held that a per se rule would be applied to boycotts only when there was evidence of an anticompetitive motive, a commercial purpose rather an industry self-regulation, and coercive economic pressure. St. Bernard General Hospital v. Hospital Service Association, 712 F.2d 978 (5th Cir. 1983). When there is no evidence of exclusionary anticompetitive purpose, intent or conduct, a rule of reason generally applies. American Medical Association v. United States, 130 F.2d 233 (D.C. Cir. 1942), affd. 317 U.S. 519, 63 S.Ct. 326, 89 L.Ed. 434 (1943).

In the proposed drug bid program there is no obvious evidence that the states or the provider-pharmacists are getting together and refusing to deal with certain drug manufacturers for an anticompetitive purpose. The articulated reason for encouraging use of the successful bidder's brand by the states is to keep costs paid for these drugs at a minimum. The intent to contain costs is not a refusal to deal but rather an intent to obtain the most competitive price and thus to promote and encourage competition among suppliers.

Using the rule of reason analysis, cost containment represents a valid competitive purpose. Reasonable contract terms and free and open access to the bidding process will lessen the possibility of a successful boycott claim against the states. However, the fact that only one manufacturer will be approved for each drug, even if more than one drug manufacturer submits the same low bid, undermines this cost containment argument and purpose. Rather, the purpose of accepting only one manufacturer appears to be either administrative ease or an effort to increase the bargaining power of the states. We strongly suggest that price containment purposes remain the rationale and primary focus of the drug bidding program. Each and every manufacturer of a required drug should be given an equal opportunity and be encouraged to compete for this business. No intent to exercise exclusionary anticompetitive pressure should be evidenced or contemplated by participating states. If the states are satisfied that the bid price of more than one brand is the lowest price they can expect or get, it may be advisable to award the business to more than one manufacturer.

The proposed drug bid program also resembles a requirement contract, which is defined as "[a contract in which] one agrees to buy, for sufficient consideration, all the merchandise of a designated type which the buyer may require for use . . . one in which a party agrees to supply a specific good which another party may need during a certain period for an agreed price." Blacks Law Dictionary 1172 (5th ed. 1979). In the proposed bid program, the state agrees to ultimately pay the price of any drug used by a benefit recipient if that recipient uses the brand of a successful bidder. Thus, the insurer-state agrees to purchase all drugs of a particular type that it requires from one manufacturer. Requirement contracts are examples of non-price vertical restraints. The risk of antitrust problems increase in relation to the relative market power created by a requirements contract. Vakerics, "Antitrust Principles" § 7.1 (1988).

A requirement contract may violate antitrust law if an arrangement substantially lessens interbrand competition and competitors are seriously hindered or foreclosed from an available market for a significant period of time. See Tampa Electric Company v. Nashville Coal Company, 365 U.S. 320, 81 S.Ct. 623, 5 L.Ed.2d 580 (1961); Standard Oil Company of California v. United States, 337 U.S. 293, 69 S.Ct. 1051, 93 L.Ed. 1371 (1949). Several federal courts have examined the concept of exclusive dealing or requirement contracts in the health care field. These cases evidence a willingness to permit these arrangements if competition is not substantially lessened or a relevant market monopolized. See DosSantos v. Columbus-Cuneo-Cabrini Medical Center, 684 F.2d 1346 (7th Cir. 1982); White and White, Inc. v. American Hospital Supply Corp., 540 F.Supp. 951 (Mich. 1982), rev'd on other grnds, 723 F.2d 495 (6th Cir. 1983).

In Medical Arts Pharmacy of Stanford, Inc. v. Blue Cross & Blue Shield of Conn., Inc., 518 F.Supp. 1100 (D. Conn. 1981), aff'd per curiam, 675 F.2d 502 (2d Cir. 1982), the district court found that the defendant insurer was the purchaser even though the insureds actually used and obtained the drug. The second circuit court seems to imply that if market share is large enough there may be sufficient monopsony power exercised by one large buyer to sustain a competitive seller's claim that a pharmaceutical purchasing agreement obtained without collusion could be anticompetitive and a violation of the Sherman Act. See also Sutliff, Inc. v. Donovan Cos., 727 F.2d 648, 655 (7th Cir. 1984); Pan-Islamic Trade Corp. v. Exxon Corp., 632 F.2d 539, 547 (5th Cir. 1980); Quality Auto Body, Inc. v. Allstate Ins. Co., 660 F.2d 1195 (7th Cir. 1981) cert. den. 455 U.S. 1020 (1982). (Monopsony; "a condition of the market in which there is but one buyer for a particular commodity." Blacks Law Dictionary 908 (5th ed. 1979).)

Most joint buying arrangements have potential efficiencies which remove them from per se violation of antitrust laws. Under the rule of reason, agreements or combinations may be prohibited if they prejudice the public interest by unduly restricting competition or obstructing the course of trade. Reazin v. Blue Cross and Blue Shield of Kansas, Inc., 635 F.Supp. 1287 (Kan. 1986). In a 1987 paper presented to the National Health Lawyers Association Conference on Antitrust Law in the Health Care Field, Michael L. Denger stated that the Federal Trade Commission considers government insurance programs to be purchasers of health care services, thus making such programs part of a relevant market. However, Mr. Denger noted that membership in a prepaid prescription drug organization making up less than 30 percent of the retail pharmaceutical sales in a geographic market will probably not be challenged by the Justice Department. Other authorities believe obtaining more than 17 to 20 percent of a relevant or geographic market will result in an antitrust law violation. It therefore becomes necessary to determine the geographic market for each drug and of each manufacturer in the bid program and what percentage of the relevant market will be given to the winning manufacturer as a result of the proposed bid program. This requires detailed factual information concerning the amount of a particular type of drug sold nationally, and in each participating state or area, and what percentage of those sales could, pursuant to this bid program, be given exclusively to the winning manufacturer. When the market share does not confer market power, anticompetitive claims become less plausible. However, antitrust laws may prohibit the proposed bid program if it allows one manufacturer to obtain an unusually large share of a relevant market, thus essentially reducing or precluding all helpful competition. The length of time that the agreement will allow the winning manufacturer to obtain this market share will also be relevant.

Unless a substantial share of a relevant market is foreclosed for a significant period of time, or unless there is an anticompetitive purpose or intent, an exclusive dealing or requirements contract will generally not present antitrust problems under a rule of reason analysis. Vakerics at § 7.09. We therefore suggest that any agreement entered into between the states or between an individual state and a pharmaceutical manufacturer be for a limited time period and initially allow every manufacturer equal access to this particular market. Once the proposed bid program and the degree of state participation is determined, an analysis of the pertinent market data can be made. It is our opinion that, under the rule of reason, unless there is an anticompetitive intent or a large percentage of the entire market for each particular drug will be foreclosed to other manufacturers for a significant period of time, the proposed drug bid program does not represent impermissible large scale buying or a prohibited requirement contract.

15 U.S.C. § 13(a) discusses price discrimination. Most recent price discrimination cases do not involve governmental prosecution, but rather, are brought by parties allegedly harmed by the behavior. Illegal price discrimination may be alleged by nonparticipating states, pharmaceutical companies who lose business, or members of the public or provider-pharmacists who do not receive the same price. Without specific information we cannot discuss the merits or standing of such challenges. Generally, any unwarranted price favoritism shown by suppliers to larger purchases not based on permissible justifications or defenses may be a violation of antitrust laws. See Gianelli Distributing Company v. Beck and Company, 172 Cal.App.3rd 120, 219 Cal. Rptr. 230 (1985); Jefferson County Pharmaceutical Association Inc. v. Abbbott Laboratories, 460 U.S. 150, 103 S.Ct. 1011, 74 L.Ed.2d 882 (1983); Portland Retail Drug Association v. Kaiser Foundation Health Plan, 662 F.2d 641 (9th Cir. 1981).

The price paid by the pharmacist and the patient-purchaser for each particular drug is not necessarily altered by the drug bid program. Rather, the drug bid program establishes the ultimate price that the state insurer will pay for the drug. The same drug (with the same shipping, manufacturing and other associated costs) will ultimately be made available to the state at a potentially different and lower price than the price paid by others. The provider-pharmacist will not necessarily be charged less for the drugs used by

Medicaid/MediKan recipients. Ultimately, however, others may pay more for the same drug.

15 U.S.C. § 13b permits rebates from a cooperative association to its members, producers, or consumers, but rebates may not be used to violate price discrimination laws. See Bargain Car Wash, Inc. v. Standard Oil Company, 466 F.2d 1163 (7th Cir. 1972). The fact that the states are paying a potentially lower price for the same drugs may not represent price discrimination if a valid defense can be claimed. The defendant (often the supplier) in an antitrust case can rebut a claim of illegal price discrimination by showing that there are lower costs in serving this particular purchaser, changing conditions allow a change in price, or competition is met and justifies the lower price. See Hansen, "Robinson-Patman Law", LI Fordham L. Rev. 113 (1983).

Prices set or obtained by governmental entities may not represent price discrimination if the activity is of a governmental nature. Generally, the Robinson-Patman Act does not apply to sales made to the government. See Gaslight Company of Columbus v. Georgia Power Company, 313 F.Supp. 860, 440 F.2d 1135, cert. den., 404 U.S. 1062, 92 S.Ct. 732, 30 L.Ed.2d 750 reh. den., 405 U.S. 969, 92 S.Ct. 1162, 31 L.Ed.2d 244 (1970). However, governmental immunity is not extended to every act or every price set by a governmental entity. See Jefferson County Pharmaceutical Association, Inc. v. Abbott Laboratories, 460 U.S. 150, 103 S.Ct. 1011, 74 L.Ed.2d 882 (1983). Immunity from antitrust laws exists for a governmental entity if (1) the challenged restraint is one clearly articulated and affirmatively expressed by state policy and (2) the policy itself is actively supervised by the state. See Russell v. City of Kansas City, Kansas, 690 F.Supp. 947 (Kan. 1988).

Using the analysis articulated in Russell, SRS and other state agencies may be able to make a legitimate argument that involvement in drug bidding programs is immune from antitrust laws. Most social welfare agencies are given authority to administer the state's medical programs and thus the argument can be made that the legislature's authorization of that administration either contemplated the resulting anticompetitive effects or such activities were a reasonably foreseeable consequence of the authorization. However, those challenging this activity may argue that the legislature allows SRS (and other equivalent agencies) to provide medical care, not to set prices in violation of antitrust laws. Jefferson County, 460 U.S. 150, 103 S.Ct. 1011, 74

L.Ed.2d 882 (1983), involved the sale of pharmaceutical products to state and local government hospitals in competition with private pharmacies. The Court, in a five to four decision, held that these actions were not exempt from the Robinson-Patman Act. However, the opinion noted that "we are not concerned with . . . state purchases for use in traditional governmental functions . . . [nevertheless] we conclude that the exemption does not apply where a state has chosen to compete in the private retail market." Id. at 153-154. In footnote seven the court acknowledged that it was not addressing whether sales by the state to indigents were in competition with private enterprises. Thus, this remains an unresolved issue.

Kansas legislators have given SRS broad authority in the area of medical care benefits for qualified persons. This delegation has allowed SRS much regulatory and discretionary authority concerning implementation of the benefits program. If SRS authorities exercise this delegated authority by participating in the drug bid program and the legislature does not act to limit this authority, it is our opinion that, even if an antitrust law would otherwise be violated, governmental immunity may allow SRS to take part in this program. Agencies from other states who wish to participate in the proposed drug bid program must individually examine whether their state's policies and enabling acts authorize participating in such a program and whether the state actively supervises its implementation.

In conclusion, although the proposed bid program raises serious antitrust questions, we believe it does not represent a per se violation of antitrust laws. Under a rule of reason analysis, the proposed drug bid program may survive an antitrust challenge. The drug bid program should be conducted so as to provide that (1) each manufacturer is given an equal and meaningful opportunity to compete for this business, with no voice in determining which manufacturer is selected, (2) the participant states should not be competing purchasers who conspire to fix a buying price, (3) objective bidding criteria should be maintained, (4) each participant pharmacist, benefit recipient and purchaser should remain free to select any and all pharmaceutical providers with which they wish to contract, (5) the winning manufacturer should not be allowed to possess a market power that unreasonably excludes or eliminates all competition, and (6) the terms of the agreement should be for a reasonable and limited time period. If, under the rule of reason analysis, a potential antitrust violation remains a possibility, governmental immunity may nevertheless allow the activity if: (1) each participating state agency has authority to enter into such an arrangement; (2) the state actively supervises the program; and (3) the anticompetitive results are expected or foreseeable. Specific legislative enactment allowing each aspect of the program could effectively negate most claims that the participating states violated antitrust laws.

Very truly yours,

Robert T. Stephan

ROBERT T. STEPHAN
ATTORNEY GENERAL OF KANSAS

Theresa Marcel Nuckolls

Theresa Marcel Nuckolls
Assistant Attorney General

RTS:JLM:TMN:bas

ATTACHMENT (3)

STATE OF KANSAS
Mike Hayden, *Governor*
DEPARTMENT OF SOCIAL AND REHABILITATION SERVICES
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☎ (913) 296-3271

Winston Barton
Secretary

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Special Assistant

Tim Owens
General Counsel

Ann Rollins
Public Information Director

Administrative Services
J. S. Duncan
Commissioner

Adult Services
Jan Allen
Commissioner

Alcohol and Drug Abuse Services
Andrew O'Donovan
Commissioner

Income Maintenance/ Medical Services
John Alquest
Commissioner

Mental Health/ Retardation Services
Al Nemec
Commissioner

Rehabilitation Services
Gabe Faimon
Commissioner

Youth Services
Robert Barnum
Commissioner

Enclosed is the information you requested concerning the Kansas Medicaid pharmaceutical bid and contract program. If you have questions, please call me at (913) 296-3981.

The Kansas Medicaid Bid Program for pharmaceuticals has one objective: to reduce the cost of pharmaceuticals the program pays for.

Bid programs are commonly used, and sometimes legally required for purchasing of many products and services. Both brand name and generic pharmaceutical companies respond to bid calls from many sources. For-profit and not-for-profit organizations call for, and receive, bids for pharmaceuticals. The difference between these bid programs and ours is: they take delivery of the drugs and we do not.

Our program calls for a claim from the provider, which we reimburse, to be "adjusted" by the bid winner thru a payment to the Medicaid Program. This is similar to the "chargeback" contractual systems used between manufacturers, wholesalers, and buying groups.

On the negative side of the Kansas Medicaid Bid Program for pharmaceuticals, there are three major points to consider. One is the administrative time required. Another is the provider education necessary. The third, and most time-consuming, is dealing with the opposition from manufacturers.

Administration of any program does take time and money. Programs require education and "fire fighting". Individuals and companies that do not understand the program, or who feel it goes against their self-interest, will fight and mount their own educational program in opposition. This can greatly increase the administrative time required for the program.

Any innovative program will have opposition. While, as stated above, our bid and adjustment program is similar to many other bid or chargeback programs, this concept has apparently never been implemented by a Medicaid Program. Many pharmaceutical companies are afraid it will work and they will have to compete in a different manner, or lose a sizable share of their sales.

Included for your information is a "handout" and presentation outline I used at the Region VII HCFA Program on Pharmacy Coverage Reimbursement last July.

One point to remember is that the Kansas program is "NDC Specific"; that is, the pharmacist must submit a claim for the product, by National Drug Code (NDC) number taken from the exact package dispensed, and this code must appear on the Kansas Medicaid/MediKan Drug List. Identical products from other manufacturer/labelers that do not appear on the Kansas Medicaid Drug List are noncovered.

Sincerely,

E. Eugene Stephens, R.Ph.
Manager
Pharmacy and Hearing Services
Division of Medical Programs

csl

Enclosure

cc: Joyce Sugrue

Region VII Medicaid Program Workshop
July 21, 1988

Kansas Medicaid/MediKan Pharmacy Bid Program
State Staff: Gene Stephens - Outline

I. Handout

- Philosophy - encourage competition
- Rationale - lower final cost to State
- Procedure - ask for bids
- Scope - generic and therapeutic alternatives
- Special Condition of Bid - adjustment to contract payment

II. Kansas Pharmacy Medicaid Background

- Variable Professional Fee
    - Documented individual pharmacy cost - 85th percentile ceiling
- Fee history
    - Relatively flat (compared to drug cost)
    - Cost study alternate years
    - No increase since 1985
- Cost-containment Efforts
    - EAC
        - Direct Cost - 8 companies
        - AWP
        - Package size
    - SMACs
    - Bidding
        - Generic
        - Therapeutic Alternatives

Region VII Medicaid Program Workshop
July 21, 1988

Kansas Medicaid/MediKan Pharmacy Bid Program

Philosophy:

To implement a cost containment and cost reduction procedure by encouraging competition between pharmaceutical suppliers to Medicaid Pharmacy providers.

Rationale:

Our providers frequently have a higher cost base for pharmaceuticals than many other classes of health care providers. The Medicaid/MediKan Program reimburses the provider for these higher costs.

Procedure:

To request bids from pharmaceutical companies that will reduce the final cost to the State of drugs dispensed to Medicaid/MediKan recipients, while increasing sales volume for the bid winner.

Scope:

Bids have been requested and received for both generic equivalent drugs and for therapeutic alternatives.

Note: We are not requiring or suggesting therapeutic substitution by the R.Ph. is necessary for this program.

csl
07/19/88

ATTACHMENT (4)

STATE OF KANSAS

DEPARTMENT OF ADMINISTRATION
Division of Purchases

MIKE HAYDEN,
Governor
NICHOLAS B. ROACH,
Director of Purchases

Landon State Office Building
900 Jackson
Room 102 N
Topeka, Kansas 66612-1220
(913) 296-2376

Contract No. 27601

Date Mailed: March 14, 1988

Closing Date,
2:00 p.m., April 4, 1988

Contracting
Officer: Eileen Shaw, PPS

Telephone: (913) 296-3124

NOTICE TO BIDDERS

Invitations are hereby extended for bids on the attached proposed contract.

TYPE OF CONTRACT: Open End Contract XX Contract ______

ITEM: PHARMACEUTICALS: Medicaid/MediKan Program

AGENCIES: Department of Social and Rehabilitation Services, Topeka, KS

PERIOD OF CONTRACT: May 1, 1988 through April 30, 1989

GUARANTEE: None

Specifications and conditions for bidding and bid forms are attached. The signature page and bid form are to be completed and returned in the enclosed envelope not later than the closing date and time indicated. Inquiries relative to this proposal should indicate the contract number and be directed to the above Contracting Officer.

The State reserves the right to reject any or all proposals (bids) and to waive technicalities.

OPEN END CONTRACT: An Open End Contract shall be construed as a contractual agreement between a supplier and the State of Kansas to furnish an undetermined quantity of a commodity (or service) in a given period of time. This may be guided by an estimated quantity based on previous history or other means.

CONTRACT: A Contract shall be construed as a contractual agreement between a supplier and the State of Kansas to furnish a predetermined quantity of a commodity (or service) in a given period of time.

SPECIAL CONDITIONS
FOR PHARMACEUTICALS: MEDICAID/MEDIKAN PROGRAM

KANSAS DEPARTMENT OF SOCIAL AND REHABILITATION SERVICES

1. The Kansas Department of Social and Rehabilitation Services (SRS) intends to reduce the number of covered pharmaceuticals and to be more cost effective in providing awarded pharmaceuticals through this invitation for bid. The Special Conditions are intended to cover an agreement to adjust prices of specified "Pharmaceuticals" provided to eligible recipients of the Medicaid/MediKan Program administered by the Department of Social and Rehabilitation Services to a price designated as the bid price. The adjustment is the difference between the price paid by SRS to the retail pharmacy and the price submitted by the vendor in their bid response. For information, SRS is asking for bids only from manufacturers, and not from wholesalers. See number 10 on page 3.

   State of Kansas General Conditions and Instructions on Bidding shall be construed as part of these conditions.

2. Time of Letting: Sealed bids covering this proposal will be accepted for consideration until 2:00 p.m. on April 4, 1988 and at that time will be publicly opened.

3. Awards: Awards will be made, by each item, after all bids have been tabulated and each item given thorough consideration by the Drug Utilization Review (DUR) Committee. The DUR Committee will judge which product would be least expensive overall based on per diem use of the starred items at the price bid per unit. This should ensure a fair evaluation between drugs which are not identical. SRS reserves the right to award as a group like items and/or companion items and reserves the right to award on alternate bids.

4. Submitting Bids: Each bid shall be completed on one of the attached bid forms in accordance with the Instruction Sheet and submitted in the envelope provided herewith. The bidder shall identify his bid by inserting his name and address in the space provided on the outside of the envelope. The bid shall be delivered to the Department of Administration, Division of Purchases, Landon Building, Topeka, Kansas 66612, not later than the time scheduled for the opening of the bids.

5. Contract: The successful bidders will be required to enter into a written contract with the State of Kansas.

6. Prices: Only one may be quoted for each product offered, in the packaging (unit) closest to that given in the specifications attached. See "INSTRUCTION SHEET" for quoting more than one product for the same item of the specifications. Bid prices shall remain firm for the contract period.

SPECIAL CONDITIONS - continued

7. Qualified or Conditional Bids: Vendor specified minimum order quantity conditions are considered conditional bids and are subject to rejection. Bids requiring multiple products or product lines as a condition of award will be rejected.

8. Quantities: The quantities indicated herein are estimated for the total period of the proposed contract. Estimates are based on usage by Medicaid/MediKan recipients. SRS reserves the right to reaward any drug product if the manufacturer fails to supply the estimated quantities. If estimated needs are greater or less than quoted, SRS assumes no responsibility to compensate the successful bidder for any difference in anticipated revenue.

9. Requirements and Specifications:

   (a) All products bid must conform to the specifications as designated herein.

   (b) All products for which bids are submitted must conform to the requirements of the specifications and formulae as designated herein; and where applicable must meet current standards of the U.S. Pharmacopeia, The Board of Health of the State of Kansas and/or its appropriate divisions and must be guaranteed as to meeting all requirements, regulations and comparison data as outlined in the Federal Food, Drug and Cosmetic Act and/or the Federal Food and Drug Administration. The manufacturer of products bid must have an FDA approved New Drug Application (NDA) or an approved abbreviated New Drug Application (ANDA).

   (c) The Manufacturer's name and item stock number of the manufacturer or distributor must be shown on the bid sheets for each item whether bidding on specifications or an alternate; otherwise the bid will not be considered. All bids must indicate the actual manufacturer of that product on the bid response form provided. The State Division of Purchases must be informed in writing of any change in manufacturer during the contract period. Changes in manufacturer are subject to approval by the Drug Utilization Review Committee.

   (d) The manufacturer/distributor certifies they are covered by a product liability insurance policy which includes provisions extending to the provider pharmacies and SRS.

   (e) Awards will be made on the basis of one uniform brand product for all strengths or types of package specified for a particular dosage form.

SPECIAL CONDITIONS - continued

10. Adjustment to Contract Payment: Provider pharmacies will continue to buy drugs and be reimbursed for Medicaid/MediKan prescriptions as usual. Adjustments (charge-backs) to the contract will be made by the manufacturer to SRS. A statement will be sent monthly from SRS to a successful bidder providing the following information:

    (a) Units of each awarded drug dispensed.

    (b) Amount reimbursed (by SRS) to pharmacies of each drug.

    (c) Amount calculated at bid price of each drug.

    (d) Amount owed to SRS (the difference between b and c) of each drug.

    (e) Total amount owed to SRS (by the successful bidder).

    (f) Time period covered.

    (g) Year-to-date totals.

    (h) Mailing address.

11. Identification of Payment: The manufacturer should identify the adjustment to contract payment by noting the contract number on the check.

12. Interest on Late Payments: Interest shall be charged on accounts that are 30 days overdue at the rate of 2% monthly.

13. Time Period Covered: Bid prices will be firm for one year. Successful bidders will be expected to make adjustments to the contract (in the form of payment to SRS) for Medicaid/MediKan prescriptions dispensed during that time. Adjustments (charge-backs) could be requested by SRS from an awarded vendor up to 6 months after contract period is ended based on previous dates of service which occurred during the contract period.

14. Container Size: Bids are being requested based on specific container sizes, but this is not intended to limit pharmacies to purchasing only that container size. An adjustment to the contract will be based on units dispensed and be independent from container size used by the pharmacy.

15. In the event no acceptable bids are received, SRS intends to select a single supplier for each described category based on current prices or to establish one price for each product.

SPECIAL CONDITIONS - continued

16. Pre-Bid Conference: A Pre-Bid Conference will be held for potential bidders, beginning at 3:00 p.m. on March 23, 1988 in the Division of Purchases conference room on the 1st floor of the Landon State Office Building, 900 Jackson, Topeka, Kansas.

    Attendance at the Pre-Bid Conference is not mandatory for vendors wishing to submit a bid, but all bidders are strongly encouraged to attend. Those interested in attending the conference should contact Eileen Shaw at (913) 296-3124 by Monday, March 21, 1988.

    The purpose of this conference is to allow potential bidders to ask questions arising from their review of this bid proposal. Questions will not be allowed after the Pre-Bid Conference.

17. Questions Regarding the Implementation of this Contract: All questions regarding the implementation of this contract should be submitted to:

    Katie Hauck, Administrator
    Division of Medical Programs
    Kansas Department of Social and
    Rehabilitation Services
    Docking State Office Building, 628-S
    Topeka, KS 66612
    (913) 296-3981

18. Questions Regarding the Requirements: SRS will accept questions concerning this bid proposal in writing prior to the Pre-Bid Conference. In addition, questions will be accepted at the Pre-Bid Conference. Questions that bear on substantial contractual issues will be answered in written form as an addendum to the bid proposal within five (5) working days after the conference. All organizations who received the bid proposal will receive the addendum. No questions may be submitted after the Pre-Bid Conference. Bidders shall not contact any SRS personnel regarding this bid proposal after the Pre-Bid Conference.

19. Addendum to the Bid Proposal: The state reserves the right to amend the bid proposal prior to the due date. If it becomes necessary to revise any part, an addendum shall be provided by certified mail to all potential bidders who have requested a copy. All bidders shall include acknowledgement of all addenda, as part of their bid quotation. Failure to acknowledge addenda may be grounds for disqualification of a bid quotation.

20. Termination of the Contract: SRS reserves the right to terminate this contract providing written notice has been given to the contractor at least thirty days prior to such proposed termination date.

21. Cost Liability: SRS assumes no responsibility and no liability for costs incurred by vendors prior to issuance of an agreement or contract.

PHARMACEUTICALS
INSTRUCTION SHEET

1. Enclosed are:
   1 copy Special Conditions for Pharmaceuticals: Medicaid/MediKan Program
   1 copy Bid Response Form and SRS Specifications for "Pharmaceuticals"
   1 pre-addressed envelope

2. Read Special Conditions and Specifications before making out bids.

3. The items listed on the combination Specifications and Bid Response Form are generally in alphabetical order. Please pay particular attention to the special conditions and instructions associated with all products for which bids are requested as a "therapeutic group" or "therapeutic drug class". Responses on these items must be made in the space associated with the appropriate generic name in the main listing.

4. Completing bid: All bid information must be typewritten. Make sure all information is legible. It is important that all instructions be followed accurately.

   a. Complete signature sheet by:
      1. Listing legal name of firm, telephone number, address, city, and state.
      2. Making sure form is signed and person signing indicates his title.

   b. Complete bid form as follows:
      1. Enter in this order: Brand name, manufacturer's name, manufacturer's catalog number, supplier's (bidder's) catalog number. Supplier's number alone or the use of "as specified" are not acceptable. If bidding an alternate product, list any deviations from Specifications.
      2. Bid unit price only. Under the "packaging" column show what that unit is. The unit quoted should be that given in the Specifications or as close thereto as is available in the product bid. Awards can be made on units "approximating" those given in the Specifications.
      3. On the additional blank forms provided, the bidder may offer two bids, one on a product designated in the Specifications for that item, and one on an alternate product, (not listed). (See paragraph 6 in the Special Conditions for bidding alternate products). For the purpose of establishing the total bid on the item, the high of the two bids shall be used.
      4. Remove all pages "not bid". Return only those pages of the "Bid Form" having items quoted for bid.

INSTRUCTION SHEET - continued

5. Recheck signature page and make certain that all information is filled in and that it is SIGNED by an authorized person.

6. Please note the bid specifications contain two (2) alphabetized sections. The first section contains specifications for which awards will be made by therapeutic class. The second is the main body of pharmaceutical specifications for drug products. Every attempt possible has been made to accurately reflect the estimated usage for these pharmaceuticals.

7. Bids must be delivered to the Department of Administration, Division of Purchases, Landon State Office Building, Topeka, Kansas 66612, not later than 2:00 p.m., April 4, 1988.

Contract Proposal Number 27601

ITEM: PHARMACEUTICALS: Medicaid/MediKan Program - Dept. of Social & Rehab. Services

DEPARTMENT OF ADMINISTRATION
DIVISION OF PURCHASES
LANDON STATE OFFICE BUILDING
900 Jackson, Room 102 N
TOPEKA, KANSAS 66612-1220

SIGNATURE SHEET

Gentlemen:

We submit a proposal to furnish requirements during the contract period in accordance with the specifications and Schedule of Supplies.

LEGAL NAME OF PERSON, FIRM OR CORPORATION: __________

FIRM TELEPHONE NUMBER: AREA CODE _____ LOCAL NUMBER __________

ADDRESS: __________

CITY & STATE: __________ ZIP CODE _____

S. S. or FEIN Number __________

SIGNATURE: __________

TYPED NAME OF SIGNATURE: __________

TITLE: __________

DATE: __________

If awarded a contract and purchase orders are to be directed to an address other than above, indicate mailing address and telephone number below:

ADDRESS: __________

CITY & STATE: __________ ZIP CODE _____

TELEPHONE: AREA CODE _____ NUMBER __________

STATE OF KANSAS
Department of Administration
Division of Accounts and Reports
DA-146a (Rev. 1-81)

Contract Proposal No. 27601
Page No. 8

CONTRACTUAL PROVISIONS ATTACHMENT

Important: This form contains mandatory contract provisions and must be attached to or incorporated in all copies of any contractual agreement. If it is attached to the vendor/contractor's standard contract form, then that form must be altered to contain the following provision:

> "The provisions found in Contractual Provisions Attachment (form DA-146a), which is attached hereto and executed by the parties to this agreement, are hereby incorporated in this contract and made a part hereof."

The undersigned parties agree that the following provisions are hereby incorporated into the contract to which it is attached and made a part thereof, said contract being dated the ____ day of ______________, 19__.

1. TERMS HEREIN CONTROLLING PROVISIONS
It is expressly agreed that the terms of each and every provision in this attachment shall prevail and control over the terms of any other conflicting provision in any other document relating to and a part of the contract in which this attachment is incorporated.

2. AGREEMENT WITH KANSAS LAW
All contractual agreements shall be subject to, governed by, and construed according to the laws of the State of Kansas.

3. TERMINATION DUE TO LACK OF FUNDING APPROPRIATION
If, in the judgment of the Director of Accounts and Reports, State Department of Administration, sufficient funds are not appropriated to continue the function performed in this agreement and for the payment of the charges hereunder, State may terminate this agreement at the end of its current fiscal year. State agrees to give written notice of termination to contractor at least 30 days prior to the end of its current fiscal year, and shall give such notice for a greater period prior to the end of such fiscal year as may be provided in this contract, except that such notice shall not be required prior to 90 days before the end of such fiscal year. Contractor shall have the right, at the end of such fiscal year, to take possession of any equipment provided State under the contract. State will pay to the contractor all regular contractual payments incurred through the end of such fiscal year, plus contractual charges incidental to the return of any such equipment. Upon termination of the agreement by State, title to any such equipment shall revert to contractor at the end of State's current fiscal year. The termination of the contract pursuant to this paragraph shall not cause any penalty to be charged to the agency or the contractor.

4. DISCLAIMER OF LIABILITY
Neither the State of Kansas nor any agency thereof shall hold harmless or indemnify any contractor for any liability whatsoever.

5. ANTI-DISCRIMINATION CLAUSE
The contractor agrees: (a) to comply with the Kansas Act Against Discrimination (K.S.A. 44-1001 et seq.) and to not discriminate against any person who performs work hereunder, because of race, religion, color, sex, physical handicap unrelated to such person's ability to engage in this work, national origin or ancestry; (b) to include in all solicitations or advertisements for employees, the phrase "equal opportunity employer"; (c) to comply with the reporting requirement set out at K.S.A. 1978 Supp. 44-1031; (d) to include those provisions in every subcontract or purchase order so that they are binding upon such subcontractor or vendor; (e) that a failure to comply with the reporting requirements of (c) above or if the contractor is found guilty of any violation of such act by the Kansas Commission on Civil Rights, shall constitute a breach of the contract and it may be cancelled, terminated or suspended in whole or in part by the Director of Purchases, State Department of Administration.

Parties to this contract understand that subsections (b) through (e) of this paragraph number 5 are not applicable to a contractor who employs fewer than four employees or whose contract with this agency of the Kansas state government total less than $5,000 during this fiscal year.

6. ACCEPTANCE OF CONTRACT
This contract shall not be considered accepted, approved or otherwise effective until the statutorily required approvals and certifications have been given.

7. ARBITRATION, DAMAGES, WARRANTIES
Notwithstanding any language to the contrary, no interpretation shall be allowed to find the State or any agency thereof has agreed to binding arbitration, or the payment of damages or penalties upon the occurrence of a contingency. Further, the State of Kansas shall not agree to pay attorney fees and late payment charges; and no provision will be given effect which attempts to exclude, modify, disclaim or otherwise attempt to limit implied warranties of merchantability and fitness for a particular purpose.

8. REPRESENTATIVE'S AUTHORITY TO CONTRACT
By signing this document, the representative of the contractor thereby represents that such person is duly authorized by the contractor to execute this document on behalf of the contractor and that the contractor agrees to be bound by the provisions thereof.

9. RESPONSIBILITY FOR TAXES
The State of Kansas shall not be responsible for, nor indemnify a contractor for, any federal, state or local taxes which may be imposed or levied upon the subject matter of this contract.

10. INSURANCE
The State of Kansas shall not be required to purchase, any insurance against loss or damage to any personal property to which this contract relates, nor shall this contract require the state to establish a "self-insurance" fund to protect against any such loss or damage. Subject to the provisions of the Kansas Tort Claims Act (K.S.A. 1979 Supp. 75-6101 et seq.), the vendor or lessor shall bear the risk of any loss or damage to any personal property in which vendor or lessor holds title.

Vendor/Contractor:		Agency Head/Authorized Representative:	
DATE	Signature	Date	Signature
	Title		Title

INFORMATION AND INSTRUCTIONS

This form is used to collect Small Business Procurement data. Therefore, it is necessary for the Certification Statement to be completed and the type of business be marked for each transaction.

TYPE OF BUSINESS (Please mark the appropriate box(es).		
SMALL	OTHER THAN SMALL BUSINESS	NON-PROFIT
WOMEN-OWNED	MINORITY	HANDICAPPED

CERTIFICATION STATEMENT

KSA 1984 Supp. 75-6003 et. seq., Kansas Small Business Procurement Act states a business must meet the following requirements in order to be Certified and considered a small business.

(a) MUST BE A SMALL BUSINESS. "Small business" means a business which is independently owned and operated not dominant in its field of operation and is not an affiliate or division of a larger business.

(b) MUST BE A BUSINESS. "Business" means: (1) An entity organized for profit, including but not limited to, an individual, partnership, corporation, joint venture, association or cooperative; or (2) a bona fide nonprofit organization operating primarily for the habilitation, rehabilitation or employment of handicapped persons which employs at least five handicapped persons for every nonhandicapped person who is directly engaged in the manufacture and processing of products by the nonprofit organization.

(c) MUST NOT BE DOMINANT IN ITS FIELD OF OPERATION. "Dominant in its field of operation" means exercising a controlling or major influence in a kind of business activity in which a number of businesses are engaged. The following businesses shall be deemed dominant in their field of operation and, therefore, do not qualify as small business under this program: (1) Manufacturing businesses which employ more than fifty (50) persons and have in the preceding three (3) fiscal years exceeded three million dollars ($3,000,000) gross income annually; (2) General construction businesses which in the preceding three (3) fiscal years exceeded four million dollars ($4,000,000) gross income annually; (3) All other non-manufacturing businesses which employ more than twenty-five (25) persons and have in the preceding three (3) fiscal years exceeded one million five hundred thousand dollars ($1,500,000) gross income annually.

(d) MUST NOT BE AN AFFILIATE OR DIVISION OF A LARGER BUSINESS. "Affiliate or division of a larger business" means a business which is a subsidiary of or owned in part by a larger business which is dominant in its field of operation, or which is owned in excess of twenty percent (20%) by the partners, officers, directors, majority shareholders, or their equivalent, of a larger business which is dominant in its field of operation.

(e) MINORITY. "Minority person" means a citizen of the United States who is Negro, Hispanic, Oriental, American Indian, Eskimo, or Aleut.

(f) HANDICAPPED. "Handicapped person" means any person who: (1) Has a temporary or permanent physical disability that requires the use of a wheelchair, walker, braces or crutches; (2) Has temporarily or permanently lost the use of one or both legs; (3) Is determined and certified by a physician to be severely restricted in mobility, either temporarily or permanently, by a pulmonary or cardiovascular disability, arthritic condition or orthopedic or neurological impairment, (4) Is afflicted with or subject to any physical or mental impairment, or both, whether congenital or due to an injury, disease or illness of such character the impairment constitutes a handicap in obtaining employment or in retaining employment.

(g) MINORITY BUSINESS. "Minority business" means a business which more than 50% is owned by a minority person or persons.

(h) WOMEN-OWNED. "Women-owned business" means a business which more than 50% is owned by a woman or women.

I hereby certify that my business qualifies as a small business as per the foregoing requirements, and that my responses to the solicitation are accurate to the best of my knowledge.

Signature of Business Owner

Federal Tax I. D. No., or Soc. Sec. No.

STATE OF KANSAS

DIVISION OF PURCHASES

SRS Pharmaceuticals: Medicaid/MediKan Program

Product Specifications and Bid Response Form

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Section II:	Pharmaceutical specifications for other drug products	6

STATE OF KANSAS - DIVISION OF PURCHASES
BID RESPONSE FORM

VENDOR CODE ☐

PAGE 1

CONTRACT: Pharmaceuticals: Medicaid/MediKan NO. 27601 PERIOD: From 5/1/88 Through 4/30/89

ITEM NO.	DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRICE
	HISTAMINE H2 ANTAGONIST DRUG CLASS It is the State of Kansas' intent to obtain bids for the histamine H2 antagonists noted below. Product descriptions, strengths and package sizes are noted. The Drug Utilization Review (DUR) committee will review these items as therapeutic equivalents and reserves the right to award on a group basis for one brand based on bids submitted on the starred items.				
1.	Cimetidine 200mg tablets (Tagamet)	100 btl	920 btl		
2.	Cimetidine 300mg tablets	100 btl	14,700 btl		
3.	Cimetidine 400mg tablets	60 btl	7,000 btl		
4.	*Cimetidine 800mg tablets	30 btl	1,200 btl		
5.	Cimetidine 300mg/2ml Inj., 8ml vial	1 vial	120 vial		
6.	Cimetidine 300mg/5ml Liquid	8 oz btl	925 btl		
7.	Ranitidine 150mg tablets (Zantac)	60 btl	30,000 btl		

STATE OF KANSAS - DIVISION OF PURCHASES
BID RESPONSE FORM

VENDOR CODE

PAGE 2

CONTRACT: Pharmaceuticals: Medicaid/MediKan NO. 27601 PERIOD: From 5/1/88 Through 4/30/89

EM O.	DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRICE
.	*Ranitidine 300mg tablets (Zantac)	30 btl	15,000 btl		
.	Ranitidine 25mg/ml Inj., 10ml vial	1 vial	120 vial		
.	Famotidine 20mg tablets (Pepcid)	30 btl	30,000 btl		
.	*Famotidine 40mg tablets	30 btl	15,000 btl		
.	Famotidine 10mg/ml Inj., 2ml vial	1 vial	100 vial		
.	Famotidine 10mg/ml Inj., 4ml vial	1 vial	150 vial		

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BID RESPONSE FORM

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CONTRACT: Pharmaceuticals: Medicaid/MediKan NO. 27601 PERIOD: From 5/1/88 Through 4/30/89

ITEM NO.	DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRICE
	ORAL CEPHALOSPORIN DRUG CLASS It is the State of Kansas' intent to obtain bids for the oral cephalosporins noted below. Product descriptions, strengths and package sizes are noted. The Drug Utilization Review (DUR) committee will review these items as therapeutic equivalents and reserves the right to award on a group basis for one brand based on bids submitted for 500mg capsules. Cephalexin (Keflex) or Cephradine (Anspor, Velosef)				
14.	Capsules: 250mg	100 cap/btl	2,700 btl		
15.	*Capsules: 500mg	100 cap/btl	1,800 btl		
16.	Oral Suspension: 125mg/5ml, 100ml btl	1 btl	2,600 btl		
17.	Oral Suspension: 250mg/5ml, 100ml btl	1 btl	4,500 btl		
18.	Oral Suspension: 500mg/5ml, 100ml btl	1 btl	100 btl		

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CONTRACT: Pharmaceuticals: Medicaid/MediKan NO. 27601 PERIOD: From 5/1/88 Through 4/30/89

ITEM NO.	DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRICE
	HYDROCHLOROTHIAZIDE-TRIAMTERENE COMBINATIONS It is the State of Kansas' intent to obtain bids for the products noted below. Product descriptions, strengths and package sizes are noted. The Drug Utilization Review (DUR) committee will review these items as therapeutic equivalents and reserves the right to award on a group basis for one brand based on the bids submitted.				
19.	Capsules: 25mg of hydrochlorothiazide and 50mg of triamterene (Dyazide)	1,000 btl	1,100 btl		
20.	Tablets: 50mg of hydrochlorothiazide and 75mg of triamterene (Maxzide)	500 btl	2,200 btl		

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CONTRACT: Pharmaceuticals: Medicaid/MediKan NO. 27601 PERIOD: From 5/1/88 Through 4/30/89

ITEM NO	DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRICE
	ALUMINUM HYDROXIDE, MAGNESIUM HYDROXIDE COMBINATIONS It is the State of Kansas' intent to obtain bids for the antacids noted below. Product descriptions, strengths and package sizes are noted. The Drug Utilization Review (DUR) committee will review these items and reserves the right to award on a group basis for one brand based on bids submitted on suspensions. Evaluation will be based on best dose per 15ml. Aluminum Hydroxide, Magnesium Hydroxide Combinations (Maalox, Aludrox, Delcid, Kolantyl, Maalox-TC, WinGel, others)				
21.	*Suspension	12 oz btl	62,500 btl		
22.	Tablets	100 btl	4,800 btl		

STATE OF KANSAS - DIVISION OF PURCHASES
BID RESPONSE FORM

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CONTRACT: Pharmaceuticals: Medicaid/MediKan NO. 27601 PERIOD: From 5/1/88 Through 4/30/89

ITEM NO.	DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRICE
	GENERIC DRUG SPECIFICATIONS, SECTION II The Drug Utilization Review (DUR) committee reserves the right to award on a group basis for one brand within a category based on bids submitted on the starred items.				
	Aluminum Hydroxide Gel (Amphojel)				
23.	*Suspension: 320mg/5ml	12 oz btl	2,275 btl		
24.	Suspension: 600mg/5ml	12 oz btl	1,750 btl		
	Aluminum Hydroxide, Magnesium Trisilicate, Alginic Acid, Sod. Bicarbonate Combination (Gaviscon, Gaviscon-II)				
25.	*Tablets: Alum. Hydroxide 80mg, Magnesium Trisilicate 20mg, plus other ingredients	100 btl	3,000 btl		
26.	Tablets: Alum. Hydroxide 160mg, Magnesium Trisilicate 40mg, plus other ingredients	48 btl	350 btl		

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BID RESPONSE FORM

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CONTRACT: Pharmaceuticals: Medicaid/MediKan NO. 27601 PERIOD: From 5/1/88 Through 4/30/89

ITEM NO.	DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRICE
	Artificial Tear Solutions (Isopto-Tears, Tears Plus, Tears Naturale, Soothe, others)				
27.	*Solution, ophthalmic: 15ml	1 btl	3,300 btl		
28.	Solution, ophthalmic: 30ml	1 btl	1,000 btl		
	Griseofulvin Ultramicrosize (Fulvicin PG, GrisPEG)				
29.	Tablets: 125mg	100 btl	75 btl		
30.	*Tablets: 250mg	100 btl	140 btl		
31.	Tablets: 330mg	100 btl	55 btl		
	Metolazone (Diulo, Zaroxolyn)				
32.	*Tablets: 5mg	100 btl	580 btl		

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CONTRACT: Pharmaceuticals: Medicaid/MediKan NO. 27601 PERIOD: From 5/1/88 Through 4/30/89

ITEM NO.	DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRICE
Nifedipine (Procardia, Adalat)					
33.	*Capsules: 10mg	100 btl	10,300 btl		
34.	Capsules: 20mg	100 btl	100 btl		
Nitroglycerin Patches (*Nitrodisc*, *Transderm-Nitro*, *Deponit*, Nitro-Dur II)					
35.	Patch: 2.5mg/24hr	30 box	1,100 boxes		
36.	*Patch: 5mg/24hr	30 box	7,000 boxes		
37.	Patch: 7.5mg/24hr	30 box	230 boxes		
38.	Patch: 10mg/24hr	30 box	3,700 boxes		
39.	Patch: 15mg/24hr	30 box	300 boxes		

STATE OF KANSAS - DIVISION OF PURCHASES
BID RESPONSE FORM

VENDOR CODE ☐

PAGE 9

CONTRACT: Pharmaceuticals: Medicaid/MediKan NO. 27601 PERIOD: From 5/1/88 Through 4/30/89

ITEM NO.	DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRICE
Potassium Chloride (Slow-K)					
40.	Sustained release capsules 8meq	100 btl	5,600 btl		
41.	*Sustained release capsules 10meq	100 btl	4,300 btl		
42.	Sustained release tablets 8meq	100 btl	11,200 btl		
43.	*Sustained release tablets 10meq	100 btl	11,600 btl		

STATE OF KANSAS - DIVISION OF PURCHASES
BID RESPONSE FORM

VENDOR CODE ☐

PAGE 10

CONTRACT: Pharmaceuticals: Medicaid/MediKan   NO. 27601   PERIOD: From 5/1/88 Through 4/30/89

ITEM NO.	DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRICE
Theophylline (Theo-Dur, SloPhyllin, Elixophyllin)					
44.	*Liquid: Elixir, Syrup or Solution 80mg/15ml	480mg/btl	100 btl		
45.	Sustained release capsules 125mg	100 btl	880 btl		
46.	*Sustained release capsules 250mg	100 btl	1,200 btl		
47.	Sustained release tablets 100mg	100 btl	550 btl		
48.	Sustained release tablets 200mg	100 btl	4,600 btl		
49.	*Sustained release tablets 300mg	100 btl	4,800 btl		

STATE OF KANSAS

DIVISION OF PURCHASES

GENERAL CONDITIONS AND INSTRUCTIONS ON BIDDING

A. GENERAL CONDITIONS

1. ACCEPTANCE OR REJECTION AND AWARD OF BID: The State of Kansas reserves the right to accept or reject any or all bids or parts of bids, to waive any informality or technicality in bids, and unless otherwise specified to accept any item in the bid. In case of error in extension of prices or other errors in calculation, the unit price shall govern. Award will be made to the lowest responsible bidder complying with conditions and specifications of the invitation to bid.

2. F. O. B. POINT: Unless otherwise specified, all bids will be F.O.B. DESTINATION. This term shall mean delivered to a state agency's receiving dock or other designated point as specified in the request for bids.

3. TAX: Unless otherwise specified, bid prices should not include Federal Excise Tax, State Sales Tax or Transportation Tax. The State of Kansas shall not be responsible for, nor indemnify a contractor for, any federal, state or local taxes which may be imposed or levied upon the subject matter of State purchases or leases.

4. BID AND PERFORMANCE GUARANTY: The Director of Purchases is authorized by law to prescribe the amounts of deposit or bond, if required, to be submitted with a bid or a contract and the amount of bond, if required, to be given for the faithful performance of a contract.

   When a bid and/or performance guaranty is required, such requirements will be clearly outlined in the invitation to bid.

   Unless otherwise specified, the bid and performance guaranty must be:
   (a) Certified or cashier's check, or

   (b) A Bid and Performance Bond (this form furnished upon request) payable to the State of Kansas. The Bid and Performance Bond must be filed with and approved by the Director of Purchases of Kansas prior to closing date of any quotation for which such bond is to serve as guaranty.

5. RETURN OF GUARANTY: The guaranty of the successful bidder will be returned after the contract has been completed by delivery and acceptance of, and payment for goods and/or services. The guaranty of the unsuccessful bidder will be returned after an award has been made to the successful bidder.

6. LIQUIDATED DAMAGES: If the successful bidder fails or refuses to enter into a contract or fails to provide goods and/or services in accordance with terms and conditions of an accepted bid, then the State of Kansas may require forfeiture of the guaranty as liquidated damages and/or removal from the bid list.

7. DEFAULT: Any vendor who defaults on delivery as defined in the proposal form may, at discretion of State, be barred from bidding for a period to be determined by the State.

8. NEW MATERIALS, SUPPLIES OR EQUIPMENT: Unless otherwise specified, all materials, supplies or equipment offered by a bidder shall be new, unused or of recent manufacture, first class in every respect, and suitable for their intended purpose; also, all equipment shall be assembled and fully serviced, ready for operation when delivered.

9. INSPECTION: The State reserves the right to reject, upon arrival at destination, any items which do not conform with specifications under which they were purchased. Sampling and inspection may be made on items at source of supply. Suppliers may ask for an inspection of goods at point of manufacture; however, such inspection will be made for convenience of the supplier, and the State reserves the right for final acceptance or rejection at point of delivery.

10. PATENTS: The seller shall protect the State from any and all damages or liability arising from alleged infringements of patents.

11. COMPLIANCE WITH KANSAS ACT AGAINST DISCRIMINATION: All bidders must agree and covenant as a condition of contract that they will comply, if required by law, with provisions of K.S.A. 44-1030 et seq. and will observe provisions of the Kansas Act Against Discrimination.

12. INSURANCE: The State of Kansas shall not be required to purchase any insurance against loss or damage to any personal property, nor shall the state establish a "self-insurance" fund to protect against any such loss or damage. Subject to the provisions of the Kansas Tort Claims Act (K.S.A. 1979 Supp. 75-6101 et seq.), the vendor or lessor shall bear the risk of any loss or damage to any personal property in which vendor or lessor holds title.

13. PUBLIC RECORDS: A complete public record file of each bid transaction is maintained for at least five (5) years by the Division of Purchases. After a bid is awarded and filed, the file is available for review by interested parties during regular business hours.

B. GENERAL INSTRUCTIONS TO BIDDERS

1. BID FORMS OR REQUEST FOR QUOTATION: Bids should be submitted only on forms provided by the State. The bid must be received in the office of the Division of Purchases not later than the date and time scheduled for closing of the bid.

2. EQUIVALENT BIDS: When brand names or trade names and model numbers followed by the words "or equivalent", or "or approved equal" are used in the bid invitation, it is for the purpose of item identification and to establish standards for quality, style and features. Bids on equivalent items of substantially the same quality, style and features are invited. However, to receive consideration, such equivalent bids must be accompanied by sufficient descriptive literature and/or specifications to clearly identify the units and provide for competitive evaluation.

3. **ACCEPTANCE OF BIDS:** Bids are invited on the basis that acceptance of the offer to furnish articles as described in the invitation shall constitute a contract between the bidder and the State of Kansas, which will bind the bidder to furnish and deliver articles for which the offer is accepted. If specifications and contents of the proposal cannot be complied with, a bidder may elect not to bid.

4. **SAMPLES:** Samples of items when required, must be furnished at no expense to the State; and, if not destroyed in the evaluation or testing process, will be returned at bidder's expense, if requested.

5. **UNIT PRICES:** Prices must be stated in units of quantity specified.

6. **DISCOUNT:** All offered discounts will be considered in determining the low bid.

7. **PREPARATION OF BID:** Each bid must be legible and properly signed. Prices are to be entered in spaces provided on the bid form. Mathematical extensions and totals shall be indicated where required. In cases of errors in extensions or totals, the unit price will govern.

8. **SIGNATURE OF BIDS:** Each bid must give the complete mailing address of bidder and be signed by him with his legal signature. Bids by partnerships must be signed by one of the members of the partnership or by an authorized representative. Bids by corporations must be signed in the name of the corporation followed by signature and title of the president, secretary, or other person authorized to bind it in the matter. The names of all persons signing should be typed or printed below the signature.

9. **MARKING AND MAILING BIDS:** Bids must be securely sealed in envelopes provided or other suitable envelopes addressed and marked on the outside as required by the invitation, including name and address of bidder, quotation number and closing date. Telegraphic or telephone bids are not acceptable unless specifically provided for in the bid invitation.

10. **TIME FOR RECEIVING BIDS:** All bidding will close promptly at 2:00 p.m. Central Standard or Daylight Savings Time, whichever is in effect at Topeka, Kansas, or other designated bid opening site on the date specified in the invitation to bid. Formal bids received prior to time of closing will be securely kept, unopened until closing time. The State will accept no responsibility for prematurely opening of a bid not properly identified on outside of envelope as requested.

11. **MODIFICATION OF BIDS:** Telegraphic or written modifications of bids already submitted will be accepted by the Division of Purchases if received prior to the date and hour scheduled for closing of bids.

12. **WITHDRAWAL OF BIDS:** A bid may be withdrawn on written, telegraph or personal request received from a properly identified bidder prior to the date and hour scheduled for closing of bids.

13. **BIDDERS PRESENT:** At the date and hour scheduled for closing, bid prices will be made public for information of interested bidders who may be present either in person or by representative. Such information is not to be construed as meaning low bidder has met all specifications as set out in invitation to bid.

14. **CAUSE FOR BID REJECTION:** Any bid may be rejected for justifiable reason, including but not limited to the following:

    (a) Failure of bidder to sign bid form.

    (b) Irregularities of any kind.

    (c) Alteration of bid form.

    (d) Obvious errors on part of the bidder.

    (e) Failure to submit required bid guaranty.

    (f) Failure to furnish requested pricing or other information.

    (g) Submission of a late bid.

    (h) Offering of alternates not called for in the invitation to bid.

    (i) Failure to comply with F.O.B. requirements.

15. **NOTICE OF AWARD:** Depending upon the type of purchase transaction, the Division of Purchases issues either a Purchase Order or a Contract to successful bidders.

16. **CHANGES:** Changes in any request for quotation, purchase order or contract may be made only upon written approval from the Director of Purchases.

17. **INVOICES AND PAYMENTS:** After furnishing acceptable goods or services, vendors may obtain payment by presenting invoices to the receiving state agency.

18. **DA146a:** Kansas Contractual Provisions Attachment, Form DA146a attached, must be signed and is made a part of this contract.

NOTE: Bidders should be aware that the various state agencies (Departments, Boards, Commissions, Institutions, etc.) have delegated authority for making certain small purchases of goods and services, and all opportunities to bid do not originate in the Division of Purchases.

Bids with an estimated value in excess of $10,000.00 are advertised in the Kansas Register. Interested bidders may contact Kansas Register, Secretary of State, State Capitol, Topeka, Kansas, 66612 for subscription information.

July, 1987

ATTACHMENT (5)

HCFA-MEDICAID
REGION VII

89 JUN -9 AM 10:33

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

MAY 18 1989

Charles West, P.D.
Executive Vice President
The National Association of Retail Druggists
205 Daingerfield Road
Alexandria, Virginia 22314

Dear Dr. West:

I am responding to your March 13 and March 22, 1989, letters regarding The Health Care Financing Administration's (HCFA) management of the Medicaid prescription drug benefit. I appreciate your good wishes on my appointment and apologize for the delay in my response.

The central issues which you raise relate to the history and intent of the Medicaid regulations that govern the methods and standards that apply to State Medicaid agencies' determinations of prescription drug payment rates. The specific rule that you address is the one that deals with a State's determination of "estimated acquisition costs" (EAC) now codified at 42 CFR 447.301. The rule provides that the EAC must be the State's best estimate of the costs of drug ingredients to pharmacies. This cost item is then added to a reasonable dispensing fee in order to determine the per prescription payments allowed, or which may be allowed, under a State Medicaid program.

The original Medicaid payment policy in this regard (i.e., ingredient cost plus a dispensing fee) was put into effect April 1976, when final drug payment rules took effect pursuant to a Notice of Proposed Rulemaking that was published in November 1974. The proposed rules would have required that States establish drug product costs by determining the actual acquisition costs of such products. The preamble to the proposed rules explained that most States were using average wholesale prices (AWP) as they were published in nationally recognized compendia such as the Red Book or Blue Book. The preamble language emphasized that these standard published prices are frequently inflated and in excess of actual costs to pharmacies. For this reason, State Medicaid agencies would be required to use the actual acquisition cost. However, many commentors on the proposed rule noted the administrative problems States would confront to determine the actual drug product acquisition costs. Therefore, the final rule was modified to require an "estimated acquisition cost" which was described as "the Medicaid agency's best estimate of the price generally and currently paid by providers for a drug marketed or sold by a particular manufacturer or labeler in the package size of drug most frequently purchased by providers." In addition, the preamble language reiterated that the published AWP is not an acceptable measure because it is frequently inflated and does not reflect the various incentives, sales promotions, discounts and allowances (other than discounts for cash or prompt payment) that are routine terms of purchasing in the drug marketplace.

Revised Medicaid rules for payment for prescription drugs were published in July 1987. They became effective in October 1987. In these rules EAC plus the dispensing fee serves as the aggregate upper payment limit standard against which the State program's actual prescription drug payments for single-source and certain multiple-source drugs are measured. The same basic policy and the substance and text of the regulations as they apply to EAC were retained.

Your description of the official actions of former HCFA Administrator Dr. Carolyne Davis and Inspector General Richard Kusserow concerning the revision of the Medicaid regulations is incomplete. During the period 1984-85, the Office of Inspector General urged HCFA to take action to pursue a Medicaid initiative recommended by that office. The initiative was the result of the Inspector General's Audit Agency Report which found that published AWP levels overstated the prices that pharmacies actually pay for drugs by approximately 16 percent on average. One of the recommendations was that the Medicaid regulations be revised to preclude the general use of AWP. HCFA believed that revision of the regulations should await decisions on the findings of a special task force that was appointed to review the existing prescription drug regulations. Moreover, HCFA explained that the States' use of AWP as a screen to which a percentage reduction would be applied was an acceptable method to establish the EAC.

There was also some discussion about whether a national policy should be adopted to require that the Medicaid EAC be expressed as AWP minus a specific percent. The consensus was that this, too, would require notice and comment rulemaking. Consequently, the recommendations to revise the regulations to explicitly preclude the general use of the AWP, or to define Medicaid EAC as AWP minus a specific percent, were not adopted. However, the initiative to provide States greater assistance in the determination of an appropriate EAC was adopted. Since this merely involved the application of the existing rules in light of the best available information, new rulemaking was not necessary. In fact, the Inspector General's report was sent to all State Medicaid agencies as a program issuance in September 1984.

I hope the preceding provides the necessary background, insight and clarification of the Federal requirements as they apply to the issues you raised in your letters. For these reasons, I do not believe it is appropriate to place a moratorium on HCFA's program administration activities to enforce the Medicaid prescription drug payment rules.

Sincerely,

Louis W. Sullivan
Louis W. Sullivan, M.D.
Secretary

Glossary

AAC - Actual Acquisition Cost.

This is "net/net." Inventory cost after all buying group and individual discounts, early payment discounts, free goods, credits, premiums, and chargebacks are deducted. It is very difficult to obtain an accurate AAC and to be useful, it has to be an average. As an average, AAC could be referred to as Estimated Actual Acquisition Cost, or (EAAC). Estimated Acquisition Cost (EAC) frequently has a different definition however. Refer to listed definition of EAC. The recently completed study, done for Kansas Medicaid by Myers and Stauffer, is probably the best estimate of EAAC done in recent years.

In 1988, under a contract with Kansas SRS, Myers and Stauffer started a study to define the actual acquisition cost of the 300 highest volume and highest total-cost drugs by National Drug Code (NDC). A total of 400 drug packages were studied. The study was completed in early 1989, but left some questions still unanswered, so several new investigative regressions were performed. The resulting data is currently contained in numerical and regression analysis chart format. Darrell Stauffer is currently drafting a narrative article to explain the analysis.

AAWP - Average of AWPs.

There are three pricing update services for pharmaceuticals: Blue Book, Red Book and MediSpan. Each uses different sources to average the wholesale prices. The AAWP is an average of the averages. Although not frequently used as a reference, it is probably a more accurate catalogue price list of wholesale cost averages.

AWP - Average Wholesale Price.

This term in years past meant what retail pharmacists paid to their wholesalers. Their net cost was no more than 2% below AWP for the average independent pharmacy in the post-World War II years. The chain stores reputedly received more than 2% cash discount. Generally, however, their cost savings were due to Direct Purchasing, where they could save the 16 2/3% wholesale markup. The chains did their own warehousing after purchasing huge quantities direct from the manufacturers.

In the last 20 years, wholesalers have become very competitive, giving large discounts to their better customers initially, and now to almost all customers. Wholesalers have increased their volume of sales, from two primary sources (aside from eliminating their competition). (1) The wholesalers have made it financially practical for both independents and chains to reduce or discontinue direct purchasing and use a "Prime Vendor" concept. (2) They are servicing the retail "buying group cooperatives" that have developed in the past five years. The AWP concept has remained, but discounts have lowered the net acquisition cost well below AWP.

HCFA recently completed a successful suit against Louisiana Medicaid for its reimbursement policy of using an "unmodified" AWP as Estimated Acquisition Cost (EAC). It is unknown whether HCFA will pursue the policy of requiring a discounted AWP for Medicaid since AWP is the pricing base stated for the Medicare Catastrophic Prescription Drug coverage when it goes into implementation. This dichotomy in HCFA policy (between Medicaid and Medicare) has not been explained, and it is unknown whether it will continue.

AWP Minus.

Recognizing the myth of AWP, some third party programs now use the published AWP as a baseline, and subtract a percentage, using varying formulas.

DESI - Drug Efficacy Study Implementation.

A federal study of the 1970's in which drugs were rated as effective, probably effective, possibly effective, or not effective. After final implementation, many drugs rated "less than effective" were forced off the market although many are still marketed. After October 30, 1981, the federal match was disallowed for any such drugs, and Kansas Medicaid removed them from the Drug List on November 30, 1981. New drugs have been added to the list sporadically since then.

DP - Direct Pricing.

Products are purchased direct from the manufacturer, at a cost savings over purchasing from a wholesaler. This term means the same as in the past, with the same 1 or 2% cash discount available for prompt payment. A great many pharmacies, both independent and chain, now utilize a prime vendor wholesaler rather than buying direct, and have reduced their overall costs to a level very close to DP. We still reimburse at DP for eight companies' products.

Drug Entity.

A drug, or specified combination of drugs packaged as a mixture; and defined by the generic name/names. A drug entity may be a sole source or brand name product, or it may be a multisource or generic product.

EAC - Estimated Acquisition Cost.

A figure that is defined by different sources as AWP, AWP minus, DP catalogue price, WAC plus, AAC, or a combination of these. We define it as MediSpan's listed DP for eight companies' products, and MediSpan's listed AWP for other drugs. (For FUL and SMAC drugs we reimburse the lower of the EAC or the FUL/SMAC price.).

FUL - Federal Upper Limits.

Also shown in some pricing references as HCFA FFP.

(1) A list of multisource drugs, specified by HCFA, for which we cannot reimburse more, in aggregate, than the cost would be if reimbursed at the FUL listed price.

(2) A less well-defined list of other drugs (essentially all others), either multisource not on the first list, or sole-source drugs, for which payment should not exceed acquisition cost.

The FUL system replaced the old federal MAC (Maximum Allowable Cost) and became effective in October, 1987. The second complete list of multisource FUL drugs became effective on July 1, 1988. The third new list was implemented June 1, 1989. Each successive new list, while using the same formula to arrive at the FUL price, has shown dramatic decreases on allowable reimbursement of some of the listed drugs. Each new list has also included new entities. Each new list has allowed an unrealistically short lead time to implement and notify providers.

NDC - National Drug Code.

The assigned eleven-digit number that defines the manufacturer/repackager (five digits), the drug entity (four digits), and the specific package (two digits).

SMAC - State Maximum Allowable Cost.

The "ceiling" price the Kansas Medicaid Program will reimburse for a drug entity.

U&C - Usual & Customary Cost.

The price which the pharmacy normally charges to non-Medicaid prescription clients.

WAC - Wholesaler Acquisition Cost.

Some wholesalers have scrapped AWP, and list their acquisition cost, to which they add a variable markup. Their catalogues show their cost, not their selling price to the pharmacist, which leaves questions when used as a reference point.

WAC Plus.

The WAC plus a percentage, as specified by some third party payors.

EES:csl
06/28/89

The CHAIRMAN. Thank you, Mr. Barton.

Mr. William Mincy, partner of the Lenco Group. Mr. Mincy is going to tell us about how retail pharmacists and buying groups have fared in securing discounts from the drug manufacturers.

Mr. Mincy.

STATEMENT OF WILLIAM MINCY, PARTNER, THE LENCO GROUP, TALLAHASSEE, FL

Mr. MINCY. Thank you, Mr. Chairman and distinguished members of the committee. My name is William Mincy. I'm a partner of the Lenco Group. Thank you for the opportunity to appear here today to address the issue of prescription drug prices.

During the past 5 years I've been involved in the development and operation of retail pharmacy group purchasing programs serving the needs of some 2,300 independent pharmacies throughout the Nation.

Allow me to begin by discussing the reasons why retail pharmacies have consolidated their purchases in order to negotiate competitive prices. Retail pharmacies, especially the smaller independently owned pharmacies, have found themselves faced with situations where they cannot and could not compete on equal footing with their competitors on the acquisition of pharmaceutical products.

Reasons for this situation include the fact that certain entities enjoy special pharmaceutical purchasing considerations because of their class of trade, profit, or not-for-profit status, or sheer size. Additionally, increased emphasis on cost containment by the Medicaid programs, the insurance industry, and the business community have provided incentives for retail pharmacies to seek methods to purchase pharmaceutical products at the best available prices or face economic ruin. In fact, individual retailers are paying the premium price so that these other entities can realize special preferred prices. In short, group purchasing programs were developed as a survival mechanism by the retail pharmacies themselves so that they can effectively compete and remain profitable.

It is estimated that more than 15,000 retail pharmacies currently participate in group purchasing programs throughout the Nation in an attempt to negotiate competitive prices from pharmaceutical manufacturers. The framework of the retail pharmacy group purchasing programs may vary from group to group or State to State. However, the fundamental concept of consolidating purchases and committing purchases in return for better prices remains the cornerstone of the movement.

In general, group purchasing program member pharmacies purchase certain negotiated products from specific drug wholesalers at special contract prices negotiated between the group's negotiator and participating pharmaceutical manufacturers and suppliers. These specific drug wholesalers, or what we call prime vendors, contract with group purchasing programs to purchase, warehouse, and distribute the products at these special contract prices. The prime vendor wholesaler purchases the products at the normal purchase price. Purchases between member pharmacies and wholesalers and between the wholesalers and the pharmaceutical manufacturers are tracked on specialized reports to safeguard against product diversion.

Another set of special reports, called chargeback reports, are generated by the wholesalers back to the manufacturers so that credit is given to the wholesaler for products sold to member pharmacies at the negotiated contract prices.

The benefits that member pharmacies realize from group purchasing programs include several things: No. 1, reduced product acquisition costs; No. 2, reduced total inventory investment; No. 3, increased inventory turnover and control; and No. 4, reduced product ordering and inventory management expenses. To date, group purchasing programs have provided these benefits to their respective member pharmacies in the extremely competitive, multisource or generic drug product market. Participating manufacturers offer contract prices to the group purchasing programs in return for increased market share and for promotional purposes.

Pharmaceutical manufacturers of single-source and brand name multi-source drug products have, for the most part, declined to participate with the group purchasing programs. Their reasons for nonparticipation include a perceived lack of commitment or buying discipline by the member pharmacies; number two, the class of trade that retail pharmacy is classified as; and number three, reduced profits. These reasons are quite confusing to member pharmacies and to the group purchasing program administrators in light that the majority of these same pharmaceutical manufacturers participate in contract purchasing programs with hospitals, health maintenance organizations, and mail order pharmacy companies that often compete directly with the retail pharmacies. A complete change in the manner drug products are sold and marketed will occur if pharmaceutical manufacturers decide to participate fully in group purchasing programs, benefiting consumers, retail pharmacies, and the pharmaceutical industry.

In summary, group purchasing programs have successfully provided the vehicle for retail pharmacies to compete effectively in today's health care marketplace. Pharmaceutical manufacturers have likewise benefited from increased sales and gains in market share as a result of their participation.

The continued viability of group purchasing programs will be linked to their ability to impact product sales and market share and improve member pharmacy's buying commitment.

Thank you for the opportunity to appear before the committee today. I'm prepared to answer any questions that you have.

The CHAIRMAN. Mr. Mincy, thank you.

I'm going to invoke the 3 minute rule on questions. I'll invoke the same rule myself. I will start out with a couple of questions for Mr. Barton.

In Kansas, in this very innovative program that you have, why do you think that the brand name drug manufacturers don't like the program, or conceivably even refuse to participate?

Mr. BARTON. Well, Mr. Chairman, the key reason I mentioned in my talk is the possible loss of profit. Right now, the way the Medicaid Program works, not only in Kansas but in all States, the State pays whatever the manufacturer charges the pharmacist. If his retail price is $50 for this drug a so-called "H_2 Antagonist", the

State pays it. They have nothing to gain unless they win the bid, but they're afraid of losing money. That's the key reason.

The CHAIRMAN. Would the consumer in Kansas save a great deal of money if the drug manufacturers would competitively bid or participate in this program?

Mr. BARTON. Oh, absolutely, especially in Medicaid, and if Medicare joins the program there will be a significant savings. The taxpayers of the State will be the big savers, and ultimately those are our citizens.

The CHAIRMAN. Mr. Barton, what has happened in the Kansas General Assembly on the State legislative level with regard to the program? Are there any obstacles there, or does the Kansas legislature support this concept? What is the status today?

Mr. BARTON. Well, Mr. Chairman, there's been a tremendous number of lobbyists in this State, also in your home State of Arkansas. There was a bill introduced into our legislature that was going to prohibit us from having basically a restricted formulary. The bill said that we could not restrict our formulary which had a fiscal note in Kansas of $20 million. Our total program is $27 million. A proviso was put in our appropriation bill that prohibited us from bidding drugs in Kansas. That was later removed before it finished the legislative process. So there's this tremendously strong lobby, not only in Kansas but in other States, to prohibit State Medicaid agencies from even trying a program such as this.

The CHAIRMAN. All right.

Mr. Mincy, let me shift to you if I might, just a moment, and my 3 minutes are about up. What has been the response of the drug manufacturers in dealing with these combinations, let's say, or these groups who want to purchase drugs less expensively? What's been the response of the manufacturers?

Mr. MINCY. The generic manufacturers have been extremely supportive of us, and have seen us as a viable method of them gaining market share. The brand name manufacturers have, for the most part, declined to participate because of either the class of trade issue that I've mentioned before, or they are afraid of the loss of profits that we would cause by providing these services to the retailers who constitute the majority of their purchasers.

The CHAIRMAN. All right.

I don't know if we have a chart on this, but I have a chart and I'm going to get some copies for the committee, showing what the pharmacist since 1982, at the local corner drugstore, is getting from Medicaid reimbursement to dispose prescriptions from behind the counter.[4] In 1982 he or she was getting $3.04. Today they're getting $3.32 for the same amount of time and the same work. Where the price of the drug itself in 1982 was $6.13, that same drug today is $11.07.

Now, what's going on here? The pharmacist is pretty well in a squeeze. The drug companies keep going up in their prices. Why all these price increases?

Mr. MINCY. Mr. Chairman, that's exactly the situation the pharmacists today find themselves in. We have to go out and talk to the consumer daily. We look quizzically at 11, 12, 18 percent price increases every year. And it is unfortunate that the consumer has to confront the pharmacist, and the pharmacist has to confront their wholesalers and manufacturers. We have no recourse but to pass those increases onto the consumer. That's the reason for us banding together.

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[4] See appendix 1, p. 339 for charts.

The **CHAIRMAN**. Mr. Mincy, my time is up. I may want to come back to a line of questions here.

I believe Senator Grassley is next on the list. I'm using the early bird rule. Some of our birds have left, but anyway, we'll go to Senator Grassley.

Senator **GRASSLEY**. Dennis, you described the volume discount that the Veterans Administration and the Department of Defense, are able to obtain from drug manufacturers, and you noted that the Veterans' Administration can get larger discounts when there's competition between companies marketing versions of the same pharmaceutical.

Are there differences among the single source drugs in the size of the discount that the VA is able to get, and are you able to say what factors determine the size of the discount you get? And just as a for instance, are you able to obtain such discounts on pharmaceuticals that have just been approved—by just approved I mean just a few weeks or months ago, for marketing by the Food and Drug Administration?

Mr. **STYRSKY**. That's a multianswer type question. It depends largely on the manufacturers themselves and their attitudes toward the Federal marketplace. I'm answering in reverse order.

New drugs that enter the marketplace—there are manufacturers who are very receptive to introducing those drugs immediately to our Federal supply schedule program, or even our depot program. There are also manufacturers who choose not to enter those drugs into any form of fixed price, whether it's a Government market or otherwise, and much like every other consumer, we are out there in the marketplace fighting for a best price on a local hospital-by-hospital basis.

Volume discounts range again, and that's becoming more standard practice, the discounts.

Senator **GRASSLEY**. You say it varies from company to company, and that's perfectly legitimate, because they are in a position to make the decision of who they want to do business with, and under what circumstances as far as bids are concerned. Could you speculate why some companies might, and others might not?

Mr. **STYRSKY**. It's easier to speculate——

Senator **GRASSLEY**. With a drug just off of the FDA approval list?

Mr. **STYRSKY**. It's largely, I think, due to the population, and does the drug fit the population. Will it have an effect on the training? And of course, Veterans Hospitals are a vast training ground for the future physicians in America. So they do like to see their product introduced there.

Senator **GRASSLEY**. Would there be any factor like some companies having a policy not to do this because they want to recoup the cost of research, where other companies might not be inclined to recoup that cost in a hurry?

Mr. **STYRSKY**. It could be their policy.

Senator **Grassley**. But you don't really know?

Mr. **Styrsky**. No. What we would hear is that they don't want to fill out a Government solicitation.

Senator **Grassley**. And you don't feel you know enough about it to speculate on that point?

Mr. **Styrsky**. That's correct.

Senator **Grassley**. OK.

Are there any other differences that you might think of, factors that determine the size of discount you get?

Mr. **Styrsky**. Basically our ability to analyze the marketplace and our relative position in that marketplace. That's been a big help to us.

The **Chairman**. Senator Grassley, I hate to do this, but I'm going to invoke the 3 minute rule on all of us alike. And if you will stay, in a moment we'll come back to you, if that's all right.

Senator **Grassley**. Yes, that's fine.

The **Chairman**. All right.

Senator Kohl.

Senator **Kohl**. Thank you, Mr. Chairman.

Mr. Mincy, why is it that the VA, the hospitals, other organizations are able to get drugs at prices that are negotiated and cheaper than what the retail operation—I mean what is it, is there something in the nature of the system, something——

Mr. **Mincy**. It's quizzical to me also, Senator. We have tried to provide the mechanism, the framework of bidding, distribution, of buying commitments, the same way that profit and not-for-profit hospitals work, and that the VA works that we're familiar with, and HMOs work. And for whatever reasons we're told that we don't apply, that we don't meet the criteria, or that it's against corporate policy at this time to deal with a retail pharmacy buying group or the retail pharmacies.

Senator **Kohl**. Is there some percentage as to how much of the product is sold at the retail level versus these other levels? Do you have an idea? Are you the big source of sales for them, and is that why they don't want to do business with you?

Mr. **Mincy**. Yes, sir. I think if you look at the pharmacy market, that the chain of independent pharmacy markets still constitutes the majority of how consumers receive their medications today. And certainly the pharmaceutical manufacturers receive the majority of their profits through the sale through community and chain drugstores.

Senator **Kohl**. Is it that in the nature of the business they go out and create a brand preference at the retail level, and that's how they can afford not to do business with you? Because they know you have to carry their product, and so they can take the biggest price from you, because as a result of their advertising they create that brand preference?

Mr. **Mincy**. Most of the marketing activities by pharmaceutical manufacturers are still directed toward the physician who writes the prescription. And then the pharmacist is responding to the prescription order and will stock the products that the physicians want for dispensing to the patients. So, we're responding to what the physician wants to serve his patients.

Senator **Kohl**. So do they then do it by getting the brand introduced at the level of the physician to the patient, and doing it as inducement, a price inducement, and then they're able to use that leverage at the retail level? Is this why it's happening?

Mr. **Mincy**. There's not very much price inducement at the retail level, sir, from a pharmacist's standpoint.

Senator **Kohl**. Right.

I said use the inducement at the other levels, a price inducement at the other levels to create the brand introduction, and then they don't have to induce—they don't have to use the leverage at your level, because it's already been accomplished?

Mr. **Mincy**. That's very possible, sir.

Senator **Kohl**. Well, you must have some ideas. I mean, you think about it all day long, I'm sure.

Mr. **Mincy**. My ideas, sir, are that the special prices that are given to HMOs and hospitals, and the Government and the VA and so forth, are being in effect carried by the retailers. We're paying the premium.

Senator **Kohl**. Yes.

Mr. **Mincy**. And I believe that there needs to be some investigation into that.

Senator **Kohl**. Do you agree, just quickly, Mr. Styrsky? Do you think he's somewhere close to analyzing the situation correctly?

Mr. **Styrsky**. I don't know. Maybe partially.

Senator **Kohl**. Or do you think they're just doing a bad job, and you're doing a good job?

Mr. **Styrsky**. No. I think we're talking two different systems, because we do deal in volume purchasing and storage on the part of the Government, and redistribution.

The **Chairman**. Senator Kohl, I hate to call time on you, but you can come back and ask other questions in just a moment. We're going to try to go by our rule.

I think our next Senator is Senator Warner.

Senator **Warner**. I'm going to pass for a moment.

The **Chairman**. Senator Warner is going to pass. I think, then, Senator Graham.

Senator **Graham**. Thank you, Mr. Chairman.

Mr. Barton, in your dealings with the pharmaceutical industry have you experienced any difference where you're dealing with a company that has a single source drug as opposed to those companies which are providing one of a multiple source?

Mr. **Barton**. Yes. And I wanted to make a comment on that. The generic companies have not given us any problem at all. They're very receptive to our bid program in Kansas. But the single sources, basically they don't want to talk to us. One of the reasons they don't, Senator, is that we're not buying the drug directly. We're basically a rebate program. They use that as the reason that they're not interested; they will not participate because we're not warehousing it like the Veterans' Administration is. And that's one of the reasons they won't participate. But I don't know that I can tell any major difference other than resistance from the single source brands.

Senator **Graham**. One of the charts in back of us here,[5] the one that shows different countries, indicates a very significant differential in the international price comparison. Have you explored the purchase of drugs from non-U.S. pharmaceutical firms where their drugs are authorized for use in the United States?

Mr. **Barton**. Not to any great degree. And it's interesting seeing that chart, comparing the other chart that's up there, in that the pharmaceutical companies have had a tremendous increase, while our local pharmacists has not.

And the numbers there are true. In our Medicaid Program, we pay whatever the pharmacist is charged for the drug plus a dispensing fee. In Kansas, that fee has gone up maybe 5 or 10 percent in the last 5 years. But the charts indicate, drug costs have gone up tremendously. But the Medicaid program in Kansas, has not had the money to increase the rates to the pharmacists. We've had to hold his fee low, because we have to pay the cost of the drug.

Senator **Graham**. I think the point of this chart is that for instance on the average in the European Economic Community, the weighted average of retail price per brand—I'm not certain what the base here is, but it was roughly one-third of what the same weighted average was in the United States. Are there any prohibitions on your applying your program of bidding to non-U.S. manufacturers of equivalent drugs which are authorized for use in the United States?

Mr. **Barton**. If they are FDA approved we can purchase the drugs. We have not actively gone out and sought those, but if they are FDA approved, yes, we can buy them.

Senator **Graham**. Are there any reasons why you have not explored that?

Mr. **Barton**. No, I'm not aware of any, but it's something that I'd be very interested in looking at.

Senator **Graham**. What about the Veterans Administration? Have you utilized non-U.S. pharmaceutical companies where they're providing equivalent U.S.-approved drugs?

Mr. **Styrsky**. Where they have been approved by the Food and Drug Administration, yes, we have, Senator.

Senator **Graham**. And what's been your experience in the use of non-U.S. pharmaceutical manufacturers' products?

The **Chairman**. Senator Graham, could he come back and answer that question in one moment, if we abide by our 3-minute rule? I hate to cut you off.

Senator Kassebaum is next.

Senator **Kassebaum**. I'll be glad to give a minute of my time.

The **Chairman**. All right.

She's going to yield you for a minute, Senator Graham.

Mr. **Styrsky**. The foreign manufacturers that we've utilized, we've had no problems with the product in terms of acceptance or effectiveness.

Senator **Kassebaum**. Does the VA buy a large percentage of its drugs from foreign manufacturers?

Mr. **Styrsky**. Not a large percentage, no, Senator.

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[5] See appendix 1, p. 344.

Senator **Kassebaum**. Do you know about what it is?

Mr. **Styrsky**. Of foreign manufacture, I would say it's probably less than 1 percent.

Senator **Graham**. Have you been able to get about the same discount from foreign manufacturers that you have been able to from the United States, and what is the comparable absolute cost, that is, after discount of similar drugs, U.S.-produced versus non-U.S. produced?

Mr. **Styrsky**. The foreign manufacturers that we have dealt with have been in the competitive arena, so we're not really talking about a proprietary or a sole source drug.

In being competitive, yes, they are very competitive. And in some cases, extremely competitive.

Senator **Graham**. Well, if they are very or extremely competitive, why do they only represent 1 percent of your purchases?

Mr. **Styrsky**. There aren't enough of them in the American market.

Senator **Graham**. There aren't enough foreign pharmaceutical firms that are——

Mr. **Styrsky**. They may not be holding approved NDA's or ANDA's to market in this country.

The **Chairman**. If we could come back to this line of questions from Senator Graham in a moment.

Senator Kassebaum.

Senator **Kassebaum**. Thank you.

Mr. Barton, I would like to ask, it is clear why the pharmaceutical companies have objections to the Kansas plan, but what response have you had from doctors? I would think there might be some objections from them as far as interference with their right to prescribe drugs of choice.

Mr. **Barton**. That's a very good question, Senator. We have had some resistance from the doctors, not as much as you might think, because one of the ways that we have tried to work with the doctors—we are not practicing medicine in the Medicaid agency, but if a doctor feels that a drug that's not on formulary is necessary for that client, we grant exceptions to the doctor. All he has to do is tell us why his patient should have one drug versus another, and then we will approve it. So, probably 95 percent of the doctors in Kansas are happy with the program.

Senator **Kassebaum**. Some of those who don't like this program bring up the antitrust issue. I am aware that the Attorney General in Kansas has cautiously concluded that we are not in infringement there. Nevertheless, do you have any comments regarding the possible anti-trust problems of expanding your bidding program into the much larger Medicare field? Would not there be a real danger of an antitrust worry as far as stifling competition?

Mr. **Barton**. There is some concern for some drugs, like the ulcer medicine that's used by the elderly. If we had a Medicare contract and we had a Medicaid contract that covered all States, we would probably have more than 30 percent of the market share of that drug, so there could possibly be that question. But I think that's a long way down the road. If we can get the program started, we'll worry about that later. But I don't think it's a major problem for the first 2 or 3 years.

Senator KASSEBAUM. Thank you.

The CHAIRMAN. By unanimous consent I am going to grant another minute to Mrs. Kassebaum, because you've been so generous in giving us of your time.

Senator KASSEBAUM. Well, the next question is sort of for anybody who wants to answer on the panel. And it's a little bit longer one.

It has to do with the Canadian system. And maybe I should save this for the next panel. I don't know if any of you are familiar with the system of granting royalties in lieu of a patent over a period of time?

I'll wait until the next panel.

The CHAIRMAN. I do think, Senator Kassebaum, after the next panel there will be someone qualified to talk about the Canadian system.

Senator KASSEBAUM. Well, I'll reserve my extra time for then.

The CHAIRMAN. Thank you, Senator Kassebaum.

Senator Simpson.

Senator SIMPSON. Thank you, Mr. Chairman.

It's been very interesting to listen to the Kansas experiment there. Senator Kassebaum had commented on that and talked about that.

I have been deeply involved in VA activities. I used to chair the committee, and then was the ranking member. But I ask Mr. Styrsky, how much staff do you use? How long does it take to prepare for your negotiations? What's involved? Can you give me a quick one on that, please? Is it a big operation in the VA?

Mr. STYRSKY. The Pharmaceutical Products Division consists of 20 people total. Our responsibility encompasses approximately $750 million in annual contracting. Preparing for negotiations is done about 180 days prior to the actual expiration date. And that starts in various phases; market research, past prices, current prices, and then actually sitting down and negotiating.

Senator SIMPSON. It must be an awesome process, how you determine prices offered to most-favored customers, other seemingly proprietary information, use of a formulary. Who decides which products deserve the favored spot?

Mr. STYRSKY. Well, the physician is ultimately the one who decides the product to be used in VA. Our charge is to make it available to him at the most economic price.

Senator SIMPSON. Do the pharmaceutical people have pretty good access to the physicians as they discuss those products?

Mr. STYRSKY. I'm sure they do, yes.

Senator SIMPSON. Do you think Medicare could achieve the same discount rates, 41 percent for single source prescriptions, 67 percent for multiple source? Do you think they could get that?

Mr. STYRSKY. I honestly don't know, Senator. That's a different system and I don't feel qualified to answer.

Senator SIMPSON. Is there any reason that manufacturers might not want to participate in similar negotiations with Medicare? Would they be less willing to divulge proprietary information to HCFA, or would the lure of a multibillion-dollar lock on a certain national product be too enticing?

Mr. STYRSKY. That, again, I don't think I'm qualified to answer.

Senator **Simpson**. Well, I think these are things that we need to find out. And I'm going to mess around in it myself.

The **Chairman**. Thank you. Senator Warner.

Senator **Warner**. Thank you.

Mr. Mincy, the underlying tone, what we've heard thus far—and I'm not suggesting the witnesses have provided the testimony, but in preparation of all of our papers and this hearing—is that the drug companies are out there just lying in the bushes gouging the poor people. And I've talked to a number of the major manufacturers and I don't think that intentionally is true. But I cannot get a grip on why the normal market forces of competition are not driving this market in the same directions, say, as television sets or automobiles or other commodities which we deal with. Is there a difference from other products in the competitive forces in this marketplace?

Mr. **Mincy**. Senator, some of the differences are the products themselves. The research that goes into the development of a product says that a certain chemical entity will meet a certain disease state, or a desired outcome is going to come from that particular product. There may not be any other products that can provide that same one.

Senator **Warner**. So they've got a monopoly then?

Mr. **Mincy**. To some effect. They were smart enough, they were industrious enough to go and develop a product that could meet that particular entity's need. And to that I've always applauded them, and will continue to.

Where we have been successful, and where market pressures really show a result, is in the more competitive multiple source products, where in fact we go and show them what our buying volume can be for a period of time, we show them the method of distribution, we provide reporting mechanisms so that we can protect against diversion. And many manufacturers, even some of the so-called brand name manufacturers, have participated. But it's been an arduous journey.

We've tracked the success of hospital buying groups for some 12 to 15 years. They likewise had a difficult time getting started. We've been in existence for 5 to 6 years now, and it's starting to show.

Senator **Warner**. Let's see if another witness wants to comment on just the marketplace and the forces within it, the driving competition.

Mr. **Barton**. Senator Warner, I would love to comment on that. That's a very good question you ask: Why doesn't the economic principles drive this? And one of the reasons is that physicians prescribe the medicine (and I've heard from many physicians), but they are not paying the cost.[6] There are four pharmaceutical companies, for example, that sell the ulcer medicine. They don't mind competing with each other. They're going to go out and see that provider and convince that provider their drug is best. But it's the client or the client's insurance company that's paying for that drug. The client is not the one who decides what drug is going to be used. And that's one of the reasons the economic principles will not necessarily work in the drug market.

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[6] For further information, see appendix 4, p. 570, Study of Physician Perceptions of Drug Prices.

Senator **Warner**. So the consensus is, normal economic principles just don't control this unique market?

Mr. **Barton**. Right.

You normally don't ask how much is this drug going to cost. A lot of people won't if the insurance company is paying for it.

Senator **Warner**. Anyone else want to tackle that?

[No response.]

Senator **Warner**. Let me ask in the minute left here——

The **Chairman**. You have a minute left.

Senator **Warner**. You're participating, the Public Health Service is participating in the DBA and the procurement partner. Are there some savings in the PHS system as a result of that joint effort?

Mr. **Styrsky**. PHS has received the same benefits that DVA and DOD have received. Yes, Senator.

Senator **Warner**. I thank the Chair.

The **Chairman**. Senator Warner, thank you.

Now if I might, I'm going to take 3 minutes. Let's turn once again to our friend in the bottle here, Mr. Motrin. There we have the Medicare paying $29 for that bottle of Motrin, and the VA paying $5. Now, Mr. Styrsky, has anyone from Medicare, Medicaid, HCFA, anyone else, ever come to you and said, Mr. Styrsky, how do you buy all this so cheaply, all these drugs? I mean, this is not just one, this is just an example. Have they ever asked you about this?

Mr. **Styrsky**. No, they have not.

The **Chairman**. Has there ever been any indication that there's an interest in saving some money in the Medicare program?

Mr. **Styrsky**. They have not contacted me.

The **Chairman**. Does HCFA, for example, know what Medicare is paying for this bottle of Motrin?

Mr. **Styrsky**. I don't know.

The **Chairman**. So they haven't expressed an interest, as far as you know, in finding out how you purchase so inexpensively?

Mr. **Styrsky**. No, sir, that's right.

The **Chairman**. Now, I'm going to place five letters in the record to bolster Mr. Barton. One is from Glaxo, one is Marion Laboratories, Roche Laboratories, Parke-Davis, and Bristol-Myers. The PACE Alliance was evidently trying to get some competitive bidding going on pharmaceuticals. These were dated mostly in July 1988, 1 year ago. One letter, for example, says, "currently, our policy at Glaxo is not to bid to retail pharmacies or retail pharmacy buying groups," which substantiates your claim. And this other one from Marion Laboratories says, "we will be unable to offer a quotation at this time as our current bidding policy precludes our offering quotations to organizations such as yours."

Further, Roche Laboratories stated: "Current policy does not permit us to offer prices to your trade category at this time."

And so it goes on and on, and I will place these five letters in the record at this point. I think they bear out what you have said, that they have been most uncooperative in attempting to deal.

[The five pharmaceutical company letters follow:]

MARION LABORATORIES, INC.
P.O. BOX 8480 • KANSAS CITY, MISSOURI 64114-0480 • 816-966-4000

July 19, 1988

Pace Alliance, Inc.
Retail Pharmacy Purchasing Group
600 Lawrence Ave., Suite 2A
Lawrence, KS 66044

Attention: Mr. B.K. Wyatt, RPh, President/CEO

Gentlemen:

We have received your invitation to offer quotations on a number of Marion products.

We will be unable to offer a quotation at this time as our current bidding policy precludes our offering quotations to organizations such as yours. Because the world of healthcare is undergoing many rapid changes, we are attempting to examine all options and avenues for distribution of our products before changing any of our present policies. At this time, therefore, we must respectfully decline your invitation to bid.

Thank you for contacting us.

Sincerely,

MARION LABORATORIES, INC.

Alfred A. Mannino

Alfred A. Mannino
Vice President
Corporate Affairs

JDT/rk

788a/9

PARKE-DAVIS
Division of Warner-Lambert Company

July 19, 1988

Dr. Curtis J. Woods, R.Ph.
Pace Alliance, Inc.
600 Lawrence Avenue
Suite 2A
Lawrence, KS 66044

Dear Dr. Woods:

Thank you for the opportunity to bid on the annual pharmaceutical requirements of Pace Alliance, Inc. We regret to advise you that Parke-Davis policy precludes our entering into such an arrangement at this time.

We appreciate the opportunity and thank you for your continued interest in Parke-Davis.

Sincerely,

Lisa M. Recchia
Supervisor, Pricing

LMR:atv

cc: R. J. Banchansky
A. A. Bonelli
M. E. Moran
J. T. Roberts

182 Tabor Road Morris Plains, New Jersey 07950 (201) 540-2000

BRISTOL-MYERS
U.S. PHARMACEUTICAL AND NUTRITIONAL GROUP
EVANSVILLE, INDIANA 47721-0001 TELEPHONE (812)429-5000

July 20, 1988

Pace Alliance, Inc.
Retail Pharmacy Purchasing Group
600 Lawrence Avenue, Suite 2A
Lawrence KS 66044

Gentlemen:

This will acknowledge receipt of your request dated July 14, 1988. We are pleased to have been selected by Pace Alliance, Inc. and offered an opportunity to bid. I regret, however, that at this time we are unable to comply with your request.

Current Company policy precludes our instituting bid prices with customers other than those within the already established approved guidelines. Pace Alliance, Inc. does not presently fall within those parameters.

The pharmaceutical industry, however, is undergoing a great deal of change and Mead Johnson/Bristol-Myers is no exception. Our customer policy has never been subject to more intensive evaluation than at this time, and if a policy change should result which would impact favorably on your request, you will be notified immediately.

In the interim, if I can ever be of service, please don't hesitate to call.

Sincerely,

M J Walts

M. J. Walts
Supervisor, Pricing

MJW/bb
enc.

BRISTOL LABORATORIES • BRISTOL-MYERS ONCOLOGY • BRISTOL-MYERS INSTITUTIONAL PRODUCTS
MEAD JOHNSON NUTRITIONALS • MEAD JOHNSON LABORATORIES • MEAD JOHNSON PHARMACEUTICALS

Roche Laboratories
ROCHE a division of Hoffmann-La Roche Inc.

340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial

July 20, 1988

Curtis J. Woods, R.Ph.
Vice President
Pace Alliance, Inc.
600 Lawrence Avenue, Suite 2A
Lawrence, KS 66044

Dear Mr. Woods:

Thank you for your recent invitation to bid on various pharmaceuticals.

Current policy does not permit us to offer prices to your trade category at this time. However, we would like to remain on your bidders mailing list should our policy change.

We appreciate your interest in Roche pharmaceuticals, if we may be of any further assistance, please do not hesitate to contact us.

Sincerely,

Jacqueline Sutton

Jacqueline H. Sutton
Administrator,
Pharmaceutical Bids & Contracts

JHS/ls

cc: S. Cofoni w/attachment
M. Goodson " "
J. Henry " "

Glaxo

Glaxo Inc.

July 27, 1988

Mr. Curtis J. Woods, R.Ph.
Vice President
Pace Alliance, Inc.
600 Lawrence Avenue
Suite 2A
Lawrence, KS 66044

Dear Mr. Woods:

Thank you for your solicitation for special pricing. Currently our policy at Glaxo is not to bid to retail pharmacies or retail pharmacy buying groups. Should our position change in the future, we will be happy to work with you.

Please accept our apologies and thank you for your interest in Glaxo.

Sincerely,

Dennis J. Dziak
Group Manager
Pricing Development and Contracts

DJD/ct

cc: Ted Kambour
Nancy Benevento

Five Moore Drive, P.O. Box 13358 Research Triangle Park, NC 27709 • Telex 802813 • Telephone (919) 248-2100

The **Chairman**. Now, once again I'm going to yield back my 12 seconds, and we'll start at the first, Senator Grassley.

Senator **Grassley**. Well, just one question.

Dennis, can you give us some sense of the magnitude of VA purchases that would allow you to negotiate such volume discounts as you do? I don't think that's been brought out. What percentage of the market, or how much do you buy?

Mr. **Styrsky**. I think the key issue is how much we buy. In our system we have a redistribution, and through our depot redistribution system we purchase annually, approximately, $240 million in drugs, prescription drug products. And we do buy in larger quantities. It's very economic for the manufacturer. There are three distribution points and a single billing point. So there is an economy involved there that assists us greatly in our negotiations.

Senator **Grassley**. Do you know what percentage of the total market for prescription drugs that is in the country?

Mr. **Styrsky**. The Government market is approximately 5 percent of the total market.

Senator **Grassley**. Mr. Chairman, I'm done.

The **Chairman**. Thank you, Senator Grassley.

Senator Kohl.

Senator **Kohl**. I just have a single question here, by way of a statement and a comment.

For the single source nitroglycerin patch, which is known as Nitro Dur, according to my information, hospitals pay as little as 1 cent for 30 patches, the VA pays $4 for 30 patches, and the cost to the retail pharmacist is over $30 for 30 patches. A cent, $4, $30. Can anybody make any sense out of this? Does anybody want to tell us something about how the system works, or the equities of it, or the remedies for that?

Mr. Barton.

Mr. **Barton**. Especially in the example you gave, hospitals; most pharmaceutical companies will give hospitals their drugs free, no bidding at all, because they want the training physicians to get use to it, and student physicians to get used to prescribing that drug. And so that's one of the reasons they get it almost free, and why others don't, I don't know. I'd be glad to yield.

Mr. **Styrsky**. I would agree as far as the hospitals, it's a great source of introduction to their product.

Mr. **Mincy**. The same, Senator.

Senator **Kohl**. So, what we're getting out of this is that it is—and not necessarily to be condemned, but it's a marketing strategy that the pharmaceutical companies use, introduce the product for whatever it costs you, at its first point of usage, and then create that demand, and then exact the profit at the end level. I mean, as I say, this is not illegal. It's not necessarily incorrect. But that's the way the system works.

The **Chairman**. Thank you, Senator Kohl.

Senator Kassebaum.

Senator **Kassebaum**. I think the response of Mr. Barton to Senator Warner's question really hits the nail on the head. You can't have economic competition when your own pocketbook isn't really affected. When you've got third party providers, a person doesn't sense or feel financial responsibility. I think that sums it up.

Senator **Warner**. Could I just ask one further question?

The **Chairman**. Senator Warner.

Senator **Warner**. I'm still concerned about the uniqueness of this marketplace. What about foreign competition? We've watched the American television industry. We started it, we built it, we lost it. Automobiles—we started, we built it, and we darned near lost it. We're getting it back. Now, we've got a great industry here, before Congress gets in and meddles around perhaps with laws and regulations. I'd hate to see us lose the quality that we're getting. Maybe the price isn't good, but nobody's arguing quality, are they? We've got the best in the world.

What about foreign competition? Is that a factor in this market?

Mr. **Mincy**. It's not from my standpoint, sir.

Mr. **Barton**. It's not in ours either, but it could be. I think it very much could be.

Senator **Warner**. Are there certain laws prohibiting it? The Germans have been preeminent in chemicals and things.

Mr. **Barton**. If FDA approves it, Medicaid agencies can use it.

Senator **Warner**. They can use it. But they have not been a factor in trying to bring about a balance of prices in this market thus far?

[Shaking of heads.]

Senator **Warner**. Thank you very much.

The **Chairman**. Thank you, Senator Warner.

I want to thank the panel this morning. We're going to leave this record open for about 7 days so if there are any follow-on questions we can submit them in writing to you. And we're very, very indebted for your testimony and for your constructive education of the committee today. Thank you very much.

Our next witness, ladies and gentlemen, is Mr. Gerald Mossinghoff, who is president of the Pharmaceutical Manufacturers Association, Washington, DC. How are you, Mr. Mossinghoff? We appreciate your attendance today. We look forward to your statement, and then I'm sure the committee will have questions.

STATEMENT OF GERALD MOSSINGHOFF, PRESIDENT, PHARMACEUTICAL MANUFACTURERS ASSOCIATION, WASHINGTON, DC

Mr. **Mossinghoff**. Thank you, Mr. Chairman. I appreciate very much this opportunity to appear before this Committee, and I hope my comments will be helpful to the Committee. I do have several observations that I hope I can make on some of the graphics, Mr. Chairman, that you displayed at the beginning of the hearing.

Major diseases that are among the most chronic and intractable in our society now primarily afflict older Americans. These include lung and colon cancers, Alzheimer's disease, osteoarthritis and osteoporosis, to name just a few of the many. Recent surveys by PMA determined that research-based pharmaceutical companies have 221 medicines in human tests that are waiting approval by the Food and Drug Administration to treat 23 of these diseases. I've attached to my statement a publication which shows the exact clinical status of these 221 medicines, and I summarize them in table 1 of my statement.

Older Americans need these new medicines in development, and they need even more the advanced therapies now in the very early stages of development. Fully one-half of the $7.3 billion of private research funds being invested by PMA companies this year in research and development is devoted to medicines for diseases that primarily afflict older Americans. Figure 1 shows the total research and development expenditures of PMA companies which have doubled every 5 years since 1970, and compares those to the expenditures of the NIH for all biomedical research. This year we outstripped NIH in the dollar amount of research and development.

In human terms the new medicines that will result from our industry will have a profound effect on how long Americans live and their quality of life in their later years. But these medicines will also have an enormous economic impact. They will save billions of dollars in the rest of the health-care system.

We hope that, as the committee continues its consideration of the research-based industry, it keeps three key characteristics in mind. One is that ours is a comparatively small and highly competitive industry. If the worldwide sales of PMA companies were combined in one hypothetical company, that company would be ranked no higher than seventh among the Fortune 500. That's all the companies that PMA represents. No company commands more than 8 percent of the market, and sales of 22 companies must be combined to reach 75 percent of the market. And as Senator Warner noted, we're proud that it is an industry that has a positive trade balance rather than a negative trade balance.

Second, PMA companies devote a far higher percentage of their sales to research and development than any other high-technology industry in the United States. Last year the industry invested 16.3 percent of sales in research and development, an increase from 10 percent in 1965. The industry standard, according to recent articles, is 3.4 percent. So we're three or four times that, at least, in terms of R&D to sales.

Finally, the industry's share, and this is extremely important, of the U.S. health-care dollar has decreased sharply from 12.4 percent in 1965 to 6.8, roughly half, in 1987, as illustrated in Figure 3 of my statement.

Mr. Chairman, I hope the rest of my statement can be put in the record. I would like to use my 5 minutes to comment on some of the graphics that you displayed.

The CHAIRMAN. Feel free to do so.

Mr. MOSSINGHOFF. First I would respectfully submit, and it's with great respect, Mr. Chairman, that the me-too factor chart is pretty misleading. The ratings of A, B, and C are set by the Food and Drug Administration. *A priori,* when a drug comes in, they set that and it determines how it paces through the FDA.

In the C category are whole new classes of drugs: ACE Inhibitors, for example, approved during the 1980's and Calcium Channel Blockers, which could very well obviate very expensive bypass surgery. On one of your charts that I saw, you had Zantac, and well you should, because that's the highest volume drug sold in the world. That was a 1-C drug when it went to FDA. So I would submit that although your figures are obviously accurate, they are based on this *a priori* rating set at the beginning of the time before they've had any serious review, and they don't recalibrate it, because all it is is a method for pacing drugs through.

I might also add that we've got our Medical Director, Senior Vice President John Beary, with us. These so-called "me-too" drugs, and that's clearly something of a pejorative term that is used, have enormous differences in terms of side effects and profiles. Many people can tolerate one drug in a certain class, but not another. So I don't think the medical profession would regard these "me-too" drugs as anything like a superfluous addition. They'd regard them as a valuable part of the armamentarium.

Secondly, I would note that the $125 million that is on your chart of our advertisement is based on a study by Professor Wiggins that was done for PMA, but is independently confirmed by two or three other studies that I could cite. One was by Stanford Research Institute a very quick-look study, but that didn't consider the time value of money. And obviously when you invest money over a 10-year period, the cost to the company is more than just the out-of-pocket expense.

And then, finally, I don't believe—I again respectfully submit—that Motrin which you showed would cost the amount somehow attributed to it for Medicare, because that's off-patent. That's ibuprofen. Generic substitutes are on the market, and under the formula that the Congress adopted, the median generic price would be the one that would be paid, not $29. So, I think, while I'm not challenging the fact there may be examples, I don't think Motrin is a good example because that's an off-patent drug at this point.

Mr. Chairman, I would like to say one last thing about the prices internationally. And that is that they vary all over the lot, because all countries have different systems of regulation, drug approval, time of regulation. On page 10 of my statement, Table 2, I show the differences within the European Common Market, which is a relatively homogeneous set of 12 European countries for a basket of 100 drugs. The prices vary from $61 in Portugal to $146 in the Federal Republic of Germany. And the average comes right about in the middle.

Finally, the average earning power has to be considered. U.S. citizens pay less than at least two countries, West Germany and France, where there are very rigorous regulations, and pay less per capita for drug expenditures a year. And that's shown in table 3 of my statement and explained in detail in footnote 3 on how we reached that conclusion.

Mr. Chairman, that concludes my very brief opening statement. However there's a lot more I would like to tell the committee.

[The prepared statement of Mr. Mossinghoff follows:]

Statement

Pharmaceutical
Manufacturers
Association

GERALD J. MOSSINGHOFF

PRESIDENT

PHARMACEUTICAL MANUFACTURERS ASSOCIATION

BEFORE THE

SPECIAL COMMITTEE ON AGING

UNITED STATES SENATE

JULY 18, 1989

Mr. Chairman and Members of the Committee:

I am Gerald J. Mossinghoff, President of the Pharmaceutical Manufacturers Association. PMA represents more than 100 research-based pharmaceutical companies that discover, develop and produce most of the prescription medicines used in the United States. I appreciate this opportunity to appear before the Special Committee during these hearings. I hope my comments will be helpful to the Committee.

Mr. Chairman, as this Committee keenly appreciates, the miracle medicines invented, developed and produced by America's research-based pharmaceutical industry have been enormously successful in lengthening lives and in improving the quality of life of older Americans and of people of all ages around the world.

The death rates from many diseases have declined impressively in recent years. In the cardiovascular area -- the diseases that are the leading killers of older Americans -- the death rate has dropped 42% in the last 20 years. Medicines have played an important role in that progress, starting with the thiazide diuretics of the 1960s through the beta blockers of the 1970s to today's calcium channel blockers, ACE inhibitors and cholesterol-lowering and anti-clotting drugs.

While progress against hypertension, stroke and other cardiovascular diseases has been impressive, that group of illnesses still afflict millions of people in the prime of their seniority. And the aging of America has created new and even more demanding challenges for our whole system of health care, including the pharmaceutical industry. Major diseases that are among the most chronic and intractable in our society now primarily afflict older Americans. These include lung and colon cancers; Alzheimer's Disease; osteoarthritis, and osteoporosis, to name just a few. Recent surveys by PMA determined that companies have 221 medicines in human tests or awaiting approval by the Food and Drug Administration to treat 23 diseases that primarily strike the elderly, as summarized in Table 1. A tabulation of the overall results of the PMA surveys is attached to my statement, giving the clinical status of each new medicine.

New Medicines for Older Americans Survey

Companies	77
Medicines	221

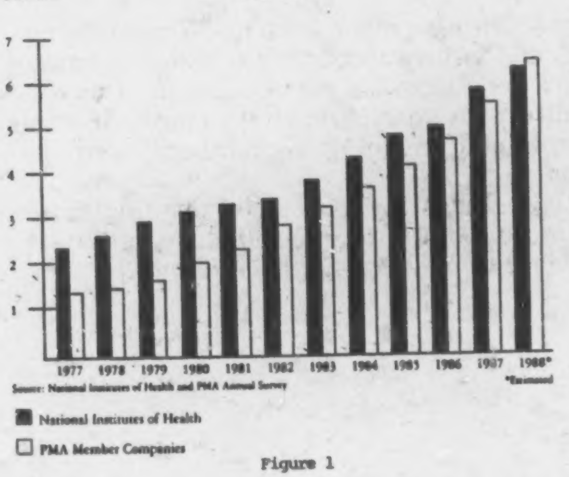
Cardiovascular Disease		Cancer		Other	
Hypertension	38	Colon	20	Depression	16
Congestive Heart Failure	28	Breast	16	Alzheimer's Disease	15
Coronary Artery Disease/ Angina	17	Lung	14	Rheumatoid Arthritis	15
Atherosclerosis	9	Skin	11	Osteoarthritis	10
Arrhythmia	8	Prostate	10	Osteoporosis	10
Peripheral Vascular Disease	8	Mouth (Oral Cavity)	1	Parkinson's Disease	6
Heart Attack (Coronary Thrombosis; Myocardial Infarction)	7	Other	25	Adult Onset Diabetes	4
Stroke (Cerebral Thrombosis)	6			Glaucoma	3
Other	2			Gout	2

Table 1

Older Americans need these new medicines now in development. And they need even more the advanced therapies now in the very early stages of research. As you recently pointed out, Mr. Chairman, we spend over $167 billion a year to treat medical conditions of the elderly, and we must "learn how to better treat and prevent the diseases that too often accompany old age." History confirms that the vast majority of new medicines needed by the elderly will come from the research-based pharmaceutical industry.

Fully half of the $7.3 billion of private funds being invested by PMA companies this year in research and development is devoted to medicines for diseases that primarily afflict older Americans. Figure 1 shows the total research and development expenditures of PMA companies since 1977, and compares those expenditures -- which have doubled every five years since 1970 -- with the total research and development spending of the National Institutes of Health for all biomedical research.

R&D Expenditures by NIH and PMA Members
1979-1988



Source: National Institutes of Health and PMA Annual Survey

Figure 1

In human terms, the new medicines that will result from our industry's R&D will have a profound effect on how long Americans will live and on their quality of life in their later years. But these new medicines will also have an enormous economic impact. Alzheimer's Disease, virtually unrecognized a generation ago, has been estimated to cost our nation more than $50 billion a year -- about twice the entire annual U.S. sales of PMA members. Former Secretary of Health, Education and Welfare Joseph A. Califano, Jr. recently estimates that "each one-month reduction of dependency for our citizens over 65 means a $4 billion savings in annual health care and custodial costs alone."

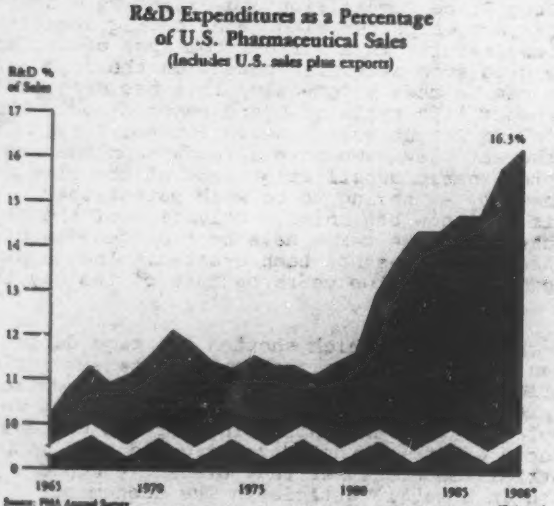
We hope that this Committee will keep in mind three key characteristics of the research-based pharmaceutical industry as these hearings proceed:

(1) It is a comparatively small and highly competitive industry. If the worldwide sales of PMA members were to be combined in one company, that company would rank no higher than seventh among the Fortune 500 companies. No company commands more than 8% of the U.S. market, and the sales of 22 companies must be combined to reach 75% of that market.

(2) PMA companies devote a far higher percentage of their sales to R&D than any other high-technology industry. Last year, the industry invested 16.3% of its sales in R&D, an increase from 10.2% in 1965, as shown in Figure 2. In a staff report issued in 1987, Chairman Waxman's House Subcommittee on Health and the Environment estimated that over 34% of the sales revenues resulting from price increases of prescription drugs from 1982 through 1986 was invested back into R&D. No other U.S. industry can match that record.

(3) The industry's share of the U.S. health-care dollar has decreased sharply from 12.4% in 1965 to 6.8% in 1987, as illustrated in Figure 3. And to my knowledge no one seriously questions the fact that this small share of the health-care expenditure pays for the most cost-effective form of medical therapy. For example, in its first 10 years, the anti-ulcer drug Tagamet saved $4 billion in the United States alone.

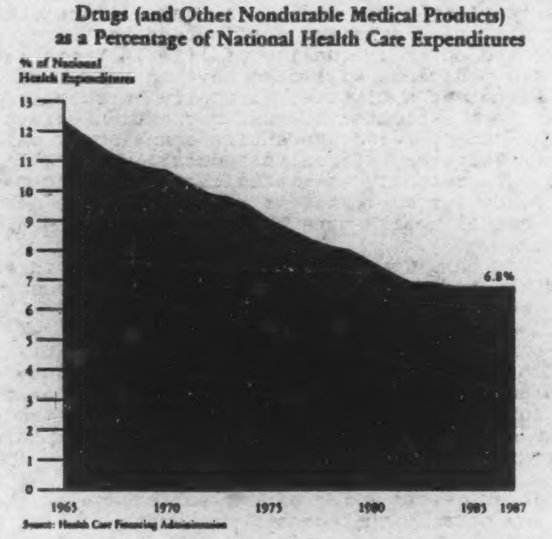
In your letters announcing this hearing, Mr. Chairman, you indicate that the Committee will consider three matters: prices of pharmaceuticals, differential pricing in the United States and price differences of pharmaceuticals internationally. Let me discuss these matters in turn.



R&D Expenditures as a Percentage of U.S. Pharmaceutical Sales
(Includes U.S. sales plus exports)

Source: PMA Annual Survey

Figure 2



Drugs (and Other Nondurable Medical Products) as a Percentage of National Health Care Expenditures

Source: Health Care Financing Administration

Figure 3

Prices of Prescription Drugs

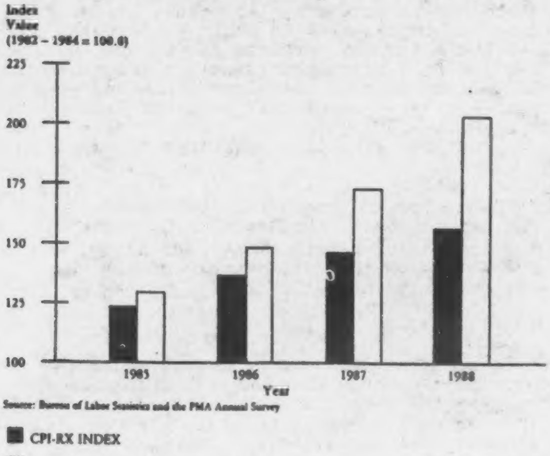
Although the cost of prescription drugs represents a declining portion of this nation's health-care expenditures, as I have noted, the prescription drug price index has increased more in the past several years than the overall Consumer Price Index. I should point out, however, that the prescription drug price index is still below the CPI established in 1967; that is, drug prices are less today than in 1967 when compared to the "all-items" component of the 1967-based CPI.

As an association of competitors, PMA does not -- and under the antitrust laws cannot -- involve itself in the pricing decisions of our members. But I can note that the period of time during which our companies can recover their enormous investment in research and development through sales revenues is being dramatically compressed due to a number of converging forces. Foremost is the unprecedented surge in competition from generic products as soon as the patent on the pioneer drug expires, spurred by the Drug Price Competition and Patent Term Restoration Act of 1984. That Act, together with generic drug substitution laws in the states, results in a virtual collapse of the market for a brand-name drug soon after the patent on the drug expires. Because generics can be made so cheaply, this has drastically shortened the product life cycle of brand-named drugs. The Drug Price Competition and Patent Term Restoration Act itself is analogous to a two-act play. We have already seen the economic effects of the pro-generic substitution part of the play. The second act of the play -- having to do with patent term restoration -- is only now beginning. Only five of the 61 pharmaceutical patents whose terms have been extended would have expired by now had extensions not been granted. And no patent has been extended more than two years because of the way the law was written.

Other major forces which shorten the time during which the companies can recover their sizeable R&D expenses include the intense competition within the research-based pharmaceutical industry to develop and market new patented drugs, long delays in FDA's approval of new drugs and increasing foreign competition from both developed countries that have targeted this industry and newly industrialized countries that blatantly condone patent piracy. As noted in a May 13 article in The Economist, ". . . during the past decade the profitable lifetime of drugs has declined while the costs of testing and marketing, which now must be worldwide in order to recoup big investments, have escalated." Professor Steven N. Wiggins of Texas A&M has estimated that the average cost to bring a new medicine from discovery to the pharmacy exceeds $125 million.

With respect to price increases of prescription drugs in recent years, the largest single factor in manufacturers' costs, but not the sole factor, has been the sharp increase in investments in R&D. Figure 4 compares the prescription drug price index, established at the 1982-84 base, to an "R&D index" based on that same starting period. R&D spending in our industry far outstrips the price index. Costs of labor, materials, taxes and promotion have also increased.

Increases in R&D vs.
Increases in Drug Prices



Source: Bureau of Labor Statistics and the PMA Annual Survey

Figure 4

Differential Pricing in the United States

The Chairman's letter of invitation to this hearing asked a number of questions concerning the sales of prescription drug products at different prices to different types or classes of buyers. The subject area generally addressed by the Chairman's letter is frequently referred to as "differential" pricing, and we feel it is very important to the Committee's deliberations that it understand the background and context of that term.

Differential pricing is regulated by the Robinson-Patman Act, enacted in 1936 to equalize the commercial power of larger purchasers and smaller, independent buyers. The Act prohibits sellers from unlawfully discriminating in price by making price differences unlawful where the effect of the differences may be to lessen competition, or to tend to create a monopoly in any line of commerce or to injure, destroy or prevent competition. Differential prices resulting from differences in the cost of manufacture, sale or delivery are not prohibited, nor are differential prices to meet competition.

In addition, the Congress in 1938 enacted the Nonprofit Institutions Act exemption to Robinson-Patman that exempts non-profit institutions, including charities, schools and hospitals, from the ban on selling at a different price so long as the purchases are for the institution's own use. This Act embodies the strong public policy in favor of allowing sellers to provide products at lower prices to charitable purchasers. Several Federal Court cases have defined the application of the Nonprofit Institutions Act to the pharmaceutical industry, with the last major case decided in 1984. Apparently the law, which has been in effect for over 50 years, is well understood by all parties in the pharmaceutical marketplace and is not generating any significant level of litigation.[1]

With respect to sales to government agencies, it is important to note the very different nature of a buyer who assumes the responsibility for distribution, warehousing, shipping and follow-up services as opposed to an individual retailer or small group of retailers who take on almost none of that burden.

In general, it seems clear that over the years many sellers, including sellers in the pharmaceutical industry, have used the flexibility afforded by the Robinson-Patman Act to meet competition in the marketplace and to observe the special status of "not-for-profit" or charitable organizations.

With regard to both domestic and international prices, your letter sets "AWP," the published Average Wholesale Price, as the standard of comparison. This can lead to quite erroneous conclusions. The 1984 Health and Human Services Inspector General Report documented the fact that most retailers purchase products at prices often well below AWP. In a six-state survey of pharmacies, the Inspector General found that 99.6% of drug purchases were made at prices averaging 16% below AWP. These drug purchases ranged from as little as .23% below AWP to as much as 42% below AWP.

In the Finance Committee and Conference Committee deliberations on the drug provisions of the Medicare Catastrophic Coverage Act of 1988, the artificial nature of AWP was noted, and provision was made in the Act, with the full support of the PMA, for Government surveys to determine actual prices.

Price Differences Internationally

Clearly, there are differences in the absolute prices of pharmaceutical products from country to country. Comparisons cannot stop at the absolute price levels alone. Because there is not a single, free, world market for pharmaceuticals, price differences country-by-country are unavoidable. Currency fluctuations are a major cause. One company's analysis shows that a hypothetical product introduced in eight foreign countries in 1982 at the exact same price of one U.S. dollar, would in 1988 be sold at prices which differed by more than 300% due to currency fluctuations alone. These price differences country-to-country -- resulting solely from currency fluctuations -- are shown in Figure 5.

Exchange Rate Effect
Product Intro 1982 at Equivalent of $1

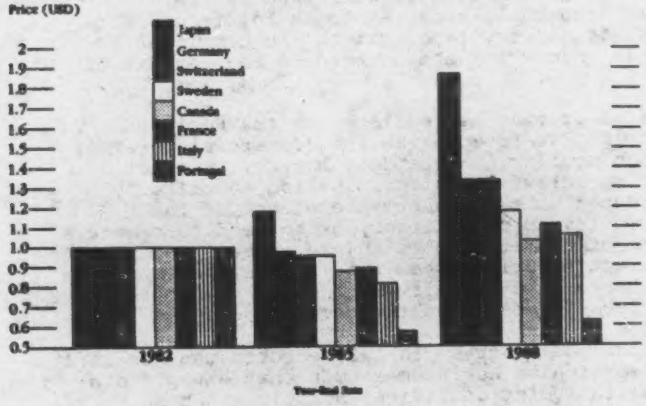


Figure 5

There are many other reasons for international price differences beyond currency fluctuations. These include differing approval times, differing standards of medical practice, differences in customary dosages, packaging differences, varying patterns of wholesale and retail markups and, of course, widely different price control and reimbursement schemes. One further major difference between the U.S. and virtually all other markets is the high cost associated with product liability and the tort system in the U.S.

In a recent study of prices on the European Common Market,[2] overall price levels for a basket of over 100 drugs varied widely, as shown in Table 2.

Countries Classified According to Prices of Drugs
When Compared With Average Retail Prices
in the European Community (in European Currency Units)

Country	Total price for the sample of selected drugs	Index EEC average is 100
Portugal	962.8	61
France	1075.9	68
Spain	1081.5	69
Greece	1115.6	71
Italy	1228.8	78
Belgium	1339.4	85
Luxembourg	1500.7	95
United Kingdom	1739.9	110
Ireland	1860.4	118
Netherlands	2067.9	131
Denmark	2227.3	141
Germany	2304.2	146

Table 2

Furthermore, the study showed that prices for individual products varied significantly in different Common Market countries. Again, several factors account for variations, both within the Common Market and for countries outside of it.

In Sweden, for example, there are no privately owned pharmacies. The Government manages the distribution system and places rigorous controls on all the participants. In my view, there is little if anything in the Swedish system that commends itself to U.S. adoption.

France also has a distribution system quite different from ours. The French Government strictly limits the number of pharmacies that can exist, basing the number on a strict ratio to the number of persons in a village or town, essentially eliminating competition between pharmacy outlets. Manufacturers' pricing is also strictly controlled. According to recent studies, this system has damaged France's indigenous research capability. Between 1961 and 1977 France was second only to the United States in drug discoveries. It has now slipped to fifth place after being overtaken by Japan, West Germany and Italy. I can report from personal conversations with French officials that efforts are underway to review their system and hopefully redress this imbalance.

In 1969 Canada amended its patent laws to establish compulsory licensing of pharmaceutical patents, rendering patents virtually useless as an incentive to innovation. The robust Canadian pharmaceutical R&D enterprise quickly atrophied. Last year, with encouragement from the U.S. Government, Canada moved toward harmonizing its patent laws with those of other developed countries by modifying the compulsory licensing provisions. That was an first important step, but the Canadian system of protection still falls short of the standards of other developed countries.

The relative purchasing power of the people of the several countries must also be considered to get a total picture of the different prices of pharmaceuticals in these countries. For example, the average French worker must work approximately two hours and 30 minutes to pay for an average French prescription, whereas a U.S. worker need only work for one hour and 11 minutes to pay for an average U.S. prescription. Even in Sweden, which has tight government controls, an average Swedish prescription represents an hour and 22 minutes of earning power.

In a similar vein, Table 3 compares the number of hours a "production worker in manufacturing" (the standard used for international comparisons by the Bureau of Labor Statistics) must work to earn the equivalent of the cost of the annual per capita drug expenditure in each of the six European countries listed in the Chairman's request for data in connection with these hearings. The number of hours of work to earn that equivalent varies from a low of 9.32 in Sweden to a high of 17.19 in West Germany. PMA's estimate of the number of hours a U.S. worker must work to pay for an annual per capita drug expenditure in the U.S. is 16.03 hours.[3]

Another major factor in international markets is that some countries, most notably Brazil, Argentina and India, blatantly condone patent piracy and provide either no patent protection or totally inadequate patent protection for our companies' inventions. In this regard, PMA has filed several petitions with the U.S. Trade Representative, and we are hopeful that those petitions and either the threat of or actual trade sanctions will help convince patent pirate countries to live up to their responsibility to protect intellectual property. PMA actively supported the intellectual property provisions of the 1988 Omnibus Trade Act, and we welcome the support key members of this Committee have provided in reinforcing the actions of the U.S. Trade Representative. We hope that those actions -- including the naming of flagrant patent-pirate nations to a so-called "priority watch list" under the special 301 procedures -- will result in those countries agreeing to live up to their responsibilities as a fair trading partner of the United States.

* * *

Mr. Chairman, that concludes my prepared statement. I would be pleased to respond to any questions you may have.

Annual Drug Expenditures Compared with
Workers Earning Power (Local Currency)

Country	1987 Drug Expenditures (billions)	1987 Population (millions)	Average Hourly Compensation	Work Hours Needed to Cover Annual Per Capita Drug Expenditure
W. Germany	31.8	60.989	30.33	17.19
France	69.5	55.396	74.68	16.74
Switzerland	2.5	6.573	25.48	14.93
Italy	12,530	57.351	15,732	13.89
U.K.	3.8	56.845	5.47	12.22
Sweden	7.5	8.383	95.99	9.32

Table 3

FOOTNOTES

[1] The landmark case interpreting the applicability of the Nonprofit Institutions Act to the pharmaceutical industry is Abbott Laboratories v. Portland Retail Druggists Association, Inc., 96 S.CT. 1305 (1976). The Supreme Court held that the Nonprofit Institutions Act exemption for purchases of supplies by a nonprofit hospital for its "own use" does not exempt all of such a hospital's drug purchases from the Robinson-Patman Act. The exempt purchases are those that reasonably may be regarded as used by the hospital for the care of its patients. The Court classifed several categories of sales and uses as being within or without the "own use" exemption.

A second major Federal Court interpretation of the Nonprofit Institutions Act was made by the Ninth Circuit in Mario de Modena dba Sixth Avenue Pharmacy v. Kaiser Foundation Health Plan, Inc., 743 F.2d 1388 (9th Cir. 1984). The Robinson-Patman Act allegations in this case were quite similar to those in Abbott Laboratories above. The defendants were a number of related corporations, including regional health plans, regional medical groups and nonprofit hospitals, as well as several pharmaceutical manufacturers. The Court of Appeals affirmed motions for summary judment finding that the defendants were not liable for violating the Robinson-Patman Act because they were within the exception to that Act created by the Nonprofit Institutions Act. The Court specifically found that drug purchases made by the Kaiser group for resale to their members were exempt from the Robinson-Patman Act. However, the Court found that purchases made by the group for resale to non-members were not within the Nonprofit Institutions Act exemption.

There were two additional Federal Court cases decided during the 1980s that are almost identical in form and substance to the Abbott Laboratories case above: Mountain View Pharmacy v. Abbott Laboratories, 630 F.2d 1383 (10th Cir. 1980) and Rudner v. Abbott Laboratories, 664 F.SUPP. 1100 (N.D. Ohio 1987). In Mountain View Pharmacy, the Court of Appeals affirmed a District Court dismissal of the complaint against all but two defendants. The Court found that the complaint did not provide defendants with sufficient notice for a responsive pleading. The case was eventually settled without trial with respect to the two remaining defendants. In Rudner, after a District Court denial of the defendants' motions for summary judgment, the case was settled with respect to all defendants without further proceedings.

There is just one other case during the last 15 years in the Federal Court system involving allegations of Robinson-Patman violations by pharmaceutical manufacturers, Jefferson County Pharmaceutical Association, Inc. v. Abbott Laboratories, 460 U.S. 150 (1983). This case was brought by a trade association of retail pharmacists and pharmacies against several manufacturers, the Board of Trustees of the University of Alabama, which operated pharmacies in connection with its hospitals, and an Alabama county hospital pharmacy. The defendants contended that sales of pharmaceutical products to state and local government hospitals for resale in competition with private retail pharmacies were exempt from the Robinson-Patman Act. The Supreme Court held that such sales are not exempt from the Act.

[2] Drug Prices and Drug Legislation in Europe, An Analyis of the Situation in the Twelve Member States of the European Communities, G. Sermeus and G. Adriaenssens, Belgian Consumers' Union, Bureau of European Unions of Consumers (BEUC)/112/89, March 1989, p. 412. PMA has not undertaken independently to verify these data.

[3] The first column--1987 Drug Expenditures--of the table "Annual Drug Expenditures Compared with Workers Earning Power (Local Currency)" consists of estimates provided by the Office of Health Economics of the Association of the British Pharmaceutical Industry. Figures include prescription and over-the-counter sales, in retail outlets and hospitals, and are shown in national currencies.

The second column--1987 Population--is from Table No. 1378, Population and Area, by Region and Country, Statistical Abstract of the United States 1988, U.S. Department of Commerce, U.S. Bureau of the Census.

The third column--Average Hourly Compensation--is from Table 3, Hourly Compensation Costs in National Currency for Production Workers in Manufacturing, 34 Countries or Areas, 1975-1988, in International Comparisons of Hourly Compensation Costs for Production Workers in Manufacturing, 1975 and 1978-1988, U.S. Department of Labor, Bureau of Labor Statistics, March 1989.

The fourth column--Work Hours Needed to Cover Annual Per Capita Drug Expenditures--was obtained by dividing drug expenditures by population, and then dividing that figure (per capita drug expenditures) by average hourly compensation.

The prescription-drug expenditures portion of the U.S. estimate of total drug expenditures was based on an unpublished PMA study, Consumer Expenditures for Drugs, 1971-1985, by G. Trapnell and J. Genuardi of Actuarial Research Corporation. The over-the-counter expenditures portion of the U.S. estimate was based on a Nielsen Market Research Survey reported in the April 17, 1989 issue of Drug Topics. The number of hours a U.S. worker must work to pay for an annual per capita drug expenditure was calculated in the same manner as the estimates for all the other countries.

IN DEVELOPMENT
NEW MEDICINES
FOR OLDER AMERICANS

Presented by the Pharmaceutical Manufacturers Association

January 1989

221 Medicines in Development to Treat 23 Diseases of Older Persons

PMA's "New Medicines for Older Americans" project consisted of a series of surveys of pharmaceutical companies to identify all medicines currently in clinical development for diseases that primarily afflict older Americans.

Here are the results of these surveys:

- 221 medicines are in human tests to treat 23 diseases that primarily afflict older persons.
- An estimated $3.6 billion will go into research on such diseases in 1989—approximately half of the industry's projected $7.3 billion research and development budget for the year.
- Cardiovascular disease leads all others as a target for research spending and drugs in development. Some 26 percent of all research funds went into cardiovascular research in 1987; and 87 drugs are being tested for use against heart disease, hypertension and stroke.
- Cancer drugs are the second largest category of drugs in development for older persons. Some 65 cancer drugs that are now in human testing are intended to treat cancers commonly associated with older persons. Colon, breast and lung cancers are the most frequently targeted cancers.
- Research also is strong on medicines for the diseases that most often result in loss of independence for older persons. The surveys showed 48 companies are developing 69 new drugs that will treat 9 diseases that often cripple and disable older persons. Among these are 15 drugs in development for Alzheimer's disease, another 25 for arthritis, 10 for osteoporosis and 6 for Parkinson's disease. Research on these diseases holds the potential for keeping the elderly independent longer and reducing the necessity for long-term care.
- Biotechnology has given a great boost to anti-cancer drug research. 29 percent of anti-cancer drugs identified are biotechnology-based. A separate PMA survey shows that half of all biotechnology drugs are for cancer. Biotechnology has become important to cancer research because it helps explain how cancers develop in the body and enables researchers to boost the body's immune system to fight cancers.

• • •

PMA sought and received the cooperation of several organizations in this project: Alliance for Aging Research, American Cancer Society, American Diabetes Association, Arthritis Foundation, College of Cardiology, and National Council on the Aging.

The "New Medicines for Older Americans" project has revealed a sizeable collection of new medicines in tests for diseases that are among the most chronic and problematic in our society. With the aging of its population, America needs research on these diseases and the medicines this research will produce.

Overview of Survey Results

PMA's survey of medicines in human testing for diseases that commonly afflict the aging found 221 individual products, 54 of which are being tested for use against more than one disease, resulting in a total of 301 research and development projects.

Following is the number of drugs being tested by disease:

Cardiovascular Disease	
Hypertension	38
Congestive Heart Failure	28
Coronary Artery Disease/Angina	17
Atherosclerosis	9
Arrhythmia	8
Peripheral Vascular Disease	8
Heart Attack (Coronary Thrombosis; Myocardial Infarction)	7
Stroke (Cerebral Thrombosis)	6
Other	2
Cancer	
Colon	20
Breast	16
Lung	14
Skin	11
Prostate	10
Mouth (Oral Cavity)	1
Other*	25
Other	
Depression	16
Alzheimer's Disease	15
Rheumatoid Arthritis	15
Osteoarthritis	10
Osteoporosis	10
Parkinson's Disease	6
Adult Onset Diabetes	4
Glaucoma	3
Gout	2
Total	**301**

**(drugs that have potential for one or more of the previous cancers; indications not yet determined)*

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IN DEVELOPMENT
NEW MEDICINES
FOR OLDER AMERICANS

Presented by the Pharmaceutical Manufacturers Association
In cooperation with
Alliance for Aging Research, American Diabetes Association, Arthritis Foundation, and National Council on the Aging

January 1989

Research on Aging Increases

69 New Drugs in Testing for 9 Debilitating Diseases

America's research-based pharmaceutical companies are developing 69 new drugs intended to treat 9 diseases that often cripple and disable older persons. These drugs are being developed by 48 companies.

Ten of the 69 drugs are being tested for more than one indication, or use, resulting in 81 separate research and development projects. These are listed separately in the attached chart.

Three diseases that are leading causes of nursing home admissions are targets for more than half of the 81 research projects identified in this PMA survey:

- 25 drugs are in development for arthritis (15 for rheumatoid arthritis and 10 for osteoarthritis),
- 15 for Alzheimer's disease, and
- 10 for osteoporosis.

Effective treatments for these three debilitating diseases will not only make life more livable in later years, but reduce the costs associated with long term care.

Also in development for diseases that primarily affect older persons are:

- 16 drugs for depression,
- 6 for Parkinson's disease,
- 4 for adult onset diabetes,
- 3 for glaucoma, and
- 2 for gout.

Adult Onset Diabetes

Alzheimer's Disease

Arthritis

Third of a series
on
New Medicines
for Older Americans.

These findings are the latest in the PMA "New Medicines for Older Americans" series that seeks to identify all medicines that have reached the human test stage for diseases that have a major impact on older persons.

Earlier surveys identified 87 drugs for heart disease, stroke and hypertension, and 65 for cancers common to older people. The 221 medicines in development by 77 companies revealed by these surveys were in 23 disease categories.

PMA member companies will invest an estimated $7.3 billion this year in research and development. It is clear from these surveys that an increasing share of this research is going into the chronic diseases associated with aging.

With these surveys, we have gained insight into the enormous commitment of the pharmaceutical industry to developing important new drugs for the treatment of diseases that plague our older citizens. In the next few years, as these products emerge from the industry's research pipeline, we will see important advances on this critical medical frontier.

Gerald J. Mossinghoff, *President Pharmaceutical Manufacturers Association*

Other Medicines for Older Americans

Alzheimer's Disease

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Zacopride	A.H. Robins (Richmond, VA)	(See also Parkinson's disease)	Phase II
Guanfacine	A.H. Robins (Richmond, VA)	(See also Parkinson's disease)	Phase II
BMY 21502	Bristol-Myers (New York, NY)	adjunct to therapy; cognition enhancement	Phase I
DuP 996	DuPont (Wilmington, DE)	cognition enhancement	Phase I
Milacemide	G.D. Searle & Co. (Chicago, IL)		Phase II
HP 029	Hoechst-Roussel (Somerville, NJ)		Phase II
HP 128	Hoechst-Roussel (Somerville, NJ)		Phase II
HOE 427	Hoechst-Roussel (Somerville, NJ)		Phase I/II
Nimotop®** Nimodipine	Miles, Inc. (Elkhart, IN)		Phase III
Acetyl-L-Carnitine	Sigma-Tau, Inc. (Newport Beach, CA)		Phase I
Oxiracetam	SmithKline Beckman (Philadelphia, PA)		Phase II/III
Capoten** Captopril	Squibb (Princeton, NJ)		Phase II
SQ 29 852**	Squibb (Princeton, NJ)		Phase II
Avan Idebenone	TAP Pharmaceuticals (N. Chicago, IL)		Phase I
Tacrine	Warner-Lambert (Morris Plains, NJ)		Phase III

Parkinson's Disease

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Zacopride	A.H. Robins (Richmond, VA)	(See also Alzheimer's disease)	Phase II
Guanfacine	A.H. Robins (Richmond, VA)	(See also Alzheimer's disease)	Phase II
Talipexole	Boehringer Ingelheim Pharmaceuticals (Ridgefield, CT)		Phase II
Motilium® Domperidone	Janssen Pharmaceutica (Piscataway, NJ)	adjunct to therapy (See also adult onset diabetes)	Phase III
SK&F 101468	SmithKline Beckman (Philadelphia, PA)		Phase II
Eldepryl Selegiline Hydrochloride	Somerset Pharmaceuticals, Inc. (Danville, NJ)		application submitted

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**approved by the FDA for other indications

Rheumatoid Arthritis

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Dysprosium Dy–165 FHMA	Cadema Medical Products (Middletown, NY)		Phase II
CGS10787D Prinomide	Ciba-Geigy (Summit, NJ)		Phase III
Voltaren®** Diclofenac sodium	Ciba-Geigy (Summit, NJ)	once-a-day regimen (See also osteoarthritis)	Phase III
Tenoxicam	Marion Laboratories (Kansas City, MO)		Phase III
CP–66, 248	Pfizer (New York, NY)	(See also osteoarthritis)	Phase III
Azulfidine EN-tabs** Sulfasalazine	Pharmacia (Piscataway, NJ)		application submitted
Tifurac Sodium	Syntex (Palo Alto, CA)	(See also osteoarthritis)	Phase II
RS–61443	Syntex (Palo Alto, CA)		Phase I
SPIRO–32® Spirogermanium	Unimed (Somerville, NJ)		Phase I
Durapro® Oxaprozin	Wyeth-Ayerst (Philadelphia, PA) G.D. Searle & Co. (Chicago, IL)	(See also osteoarthritis, gout)	application submitted
Ultradol® Etodolac	Wyeth-Ayerst (Philadelphia, PA)	(See also osteoarthritis, gout)	application submitted
XomaZyme–H65* MAb	XOMA (Berkeley, CA)		Phase I

Gout

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Durapro® Oxaprozin	Wyeth-Ayerst (Philadelphia, PA) G.D. Searle & Co. (Chicago, IL)	(See also osteoarthritis, rheumatoid arthritis)	application submitted
Ultradol® Etodolac	Wyeth-Ayerst (Philadelphia, PA)	(See also osteoarthritis, rheumatoid arthritis)	application submitted

Adult Onset Diabetes

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
HOE 490 Glimepiride	Hoechst-Roussel (Somerville, NJ)		Phase I
Statil Ponalrestat	ICI Pharmaceuticals (Wilmington, DE) Merck, Sharp & Dohme (Rahway, NJ)	adjunct to therapy; aldose reductase inhibitor	Phase III
Motilium® Domperidone	Janssen Pharmaceutica (Piscataway, NJ)	adjunct to therapy (See also Parkinson's disease)	application submitted
Alredase Tolrestat	Wyeth-Ayerst (Philadelphia, PA)		Phase III/application submitted

Osteoarthritis

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Deflazacort	Merrell Dow (Cincinnati, OH)		Phase II
CP-66, 248	Pfizer (New York, NY)	(See also rheumatoid arthritis)	Phase III
Tifurac Sodium	Syntex (Palo Alto, CA)	(See also rheumatoid arthritis)	Phase II
Durapro® Oxaprozin	Wyeth-Ayerst (Philadelphia, PA) G.D. Searle & Co. (Chicago, IL)	(See also rheumatoid arthritis, gout)	application submitted
Ultradol® Etodolac	Wyeth-Ayerst (Philadelphia, PA)	(See also rheumatoid arthritis, gout)	application submitted

Osteoporosis

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Ogen** Estropipate	Abbott Laboratories (N. Chicago, IL)		Phase III
Gestodene	Berlex Laboratories (Wayne, NJ)		Phase II
IGF-1*/**	Chiron Corporation (Emeryville, CA) Ciba-Geigy (Summit, NJ)		Phase I
Estraderm® Estradiol transdermal system	Ciba-Geigy (Summit, NJ)		Phase III
Osteo-F Fluoride	Colgate-Hoyt (Canton, MA)		Phase III
Humatrope*/** Somatropin	Eli Lilly (Indianapolis, IN)		in clinical trials
Slow-Fluoride sodium fluoride	Mission Pharmacal (San Antonio, TX)		application submitted
ORTHO-EST	Ortho Pharmaceuticals (Raritan, NJ)		Phase III
ORTHO-EST PLUS	Ortho Pharmaceuticals (Raritan, NJ)		Phase III
Salmon Calcitonin	Rorer Group (Fort Washington, PA)	intranasal dosage form; approved in injectable dosage form under brand name Calcimar®	Phase III

Rheumatoid Arthritis

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Relafen Nabumetone	Beecham Laboratories (Bristol, TN)	(See also osteoarthritis)	Phase III/application submitted
Superoxide Dismutase*	Bio-Technology General (New York, NY)	(See also osteoarthritis)	Phase I
Immuneron®* Recombinant Gamma Interferon	Biogen (Cambridge, MA)		Phase II

Glaucoma

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Optipress Carteolol	Burroughs Wellcome (Research Triangle Park, NC)		application pending
Ketanserin Ophthalmic	IOLAB Pharmaceuticals (Claremont, CA)		Phase I
Timpilo®	Merck, Sharp & Dohme (West Point, PA)		Phase III

The content of this chart has been obtained through industry sources based on the latest information. Chart current as of January 20, 1989. The information may not be comprehensive. For more specific information about a particular product, contact the individual company directly. For general information, contact the Pharmaceutical Manufacturers Association at (202) 835-3463. *(If you did not receive your own copy of this issue of "Other Medicines For Older Americans," please write to the Communications Division at the Pharmaceutical Manufacturers Association.)*

GLOSSARY

Adjunct—A substance or drug that aids or helps another become effective or more effective. An adjunct also aids the delivery of a drug to a place where it is most effective in the body.

Aldose reductase inhibitor—a category of drugs being developed to interfere with a series of biochemical and pathological reactions. Their use is intended to prevent the enzyme aldose reductase from changing blood sugar to sorbitol, interrupting the build-up of sorbitol in tissues and preventing cell destruction.

Application submitted—An application for marketing has been submitted by the company to the Food and Drug Administration (FDA).

Phase I—Safety testing and pharmacological profiling in humans.

Phase II—Effectiveness testing in humans.

Phase III—Extensive clinical trials in humans.

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Pharmaceutical
Manufacturers
Association

1100 15th Street, NW • Washington, DC 20005 • Telephone (202) 835-3400

Depression

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Aropax	Beecham Laboratories (Bristol, TN)		Phase III
Prothiaden® Dothiepin Hydrochloride	The Boots Company (Lincolnshire, IL)		Phase III
Gepirone	Bristol-Myers (New York, NY)		Phase III
Nefazodone	Bristol-Myers (New York, NY)		Phase III
Wellbutrin® Bupropion Hydrochloride	Burroughs Wellcome (Research Triangle Park, NC)		application submitted
GR50360	Glaxo (Research Triangle Park, NC)		Phase I/II
Moclobemide	Hoffmann-La Roche (Nutley, NJ)		Phase II
ICI-169369	ICI Pharmaceuticals (Wilmington, DE)		Phase II
Ritanserin	Janssen Pharmaceutica (Piscataway, NJ)		Phase II
Maxitene Femoxetine	Martec Pharmaceutical (Kansas City, MO)		Phase II
Etonin™ Etoperidone	McNeil Pharmaceutical (Spring House, PA)		Phase III
ORG 3770	Organon (West Orange, NJ)		Phase III
Sertraline	Pfizer (New York, NY)		application submitted
Fluvoxamine	Reid-Rowell, Inc. (Marietta, GA)		Phase III
Deracyn™ Tablets Adinazolam Mesylate	Upjohn (Kalamazoo, MI)		application submitted
Venlafaxine Hydrochloride	Wyeth-Ayerst (Philadelphia, PA)		Phase III

Osteoarthritis

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Bromfenac	A.H. Robins (Richmond, VA)		Phase II
Relafen Nabumetone	Beecham Laboratories (Bristol, TN)	(See also rheumatoid arthritis)	Phase III/application submitted
Superoxide Dismutase*	Bio-Technology General (New York, NY)	(See also rheumatoid arthritis)	Phase I
Voltaren®** Diclofenac sodium	Ciba-Geigy (Summit, NJ)	once-a-day regimen (See also rheumatoid arthritis)	Phase III
Ontosein® Superoxide Dismutase— Orgotein	DDI Pharmaceuticals (Mountain View, CA)		Phase III

*genetically engineered

IN DEVELOPMENT

NEW MEDICINES

FOR OLDER AMERICANS

Presented by the
Pharmaceutical Manufacturers Association

A Guide to Diseases of Older Americans

Following is a guide to the diseases of older persons that were involved in our series of surveys on "New Medicines for Older Americans."

Aging can bring with it a complex set of health problems. These diseases deprive older persons of independence by limiting their function—physically and mentally. Quality of life is affected due to pain, depression, and financial stress. Arthritis alone cost the United States $8.6 billion, according to 1984 data from the Arthritis Foundation. Great psychological and economic stress is placed on families and other caregivers. Diseases of aging deprive society of productive individuals and escalate health care costs. Some of these diseases are not well understood. In some cases, treatments are not available or have limited safety and efficacy. Often older persons must take a variety of medications to help treat their health problems, but medication to help one problem may exacerbate another. Thus there remains much to be learned about diseases of aging and the search continues for safe and effective new treatments.

ADULT ONSET DIABETES

A chronic disease characterized by abnormal insulin secretion from the pancreas, thereby causing problems in metabolizing sugar. Symptoms may include: excessive thirst, hunger, urination, and weight loss. Diet, exercise, and weight loss are often sufficient to control this disease. Insulin treatment is needed for only a minority of elderly diabetics. Oral drugs are useful in some patients. The American Diabetes Association says that nearly 3.1 million people over 65 had diabetes in 1987 and that nearly 26,000 diabetic patients over 65 were in nursing homes. More than 80,000 deaths were estimated to have been caused by diabetes in 1987. Total cost of institutional care of diabetic patients of all ages was $7.9 billion, the assocation estimates.

ALZHEIMER'S DISEASE

Chronic deterioration of all mental functions, with average onset around age 65. It is progressive and rarely reversible. Early manifestations include decrease in attention span, impaired powers of concentration, some personality change and forgetfulness. It is difficult to diagnose, so often is not recognized at an early stage. As the disease progresses, there is loss of computational ability, word-finding problems, difficulty with ordinary activities such as dressing, cooking and balancing the checkbook, then severe memory loss and ultimately, complete disorientation, social withdrawal, and loss of independence. The personality changes may include aggressive outbursts, inappropriate sexual behavior, paranoia, and depression. The "death of the mind" has been described by both patients and family members as "the most horrible death imaginable." The increasing hours of care over many years lead to family stress, marital problems, bankruptcy, and the development of physical disorders, as well as severe depression and anxiety in the caregivers. There are no medications available that reverse the primary characteristics of the disease. Drugs are frequently used to treat symptoms such as agitation, depression, and psychosis. According to the Alzheimer's Disease and Related Disorders Association, an estimated 2.5 million Americans suffer from Alzheimer's and more than 100,000 are estimated to have died of Alzheimer's in 1988. The organization says that about $40 billion–$50 billion a year is spent caring for patients at home and in nursing facilities.

ARRHYTHMIA

Abnormal heart rhythm, usually detected by an electrocardiogram. Arrhythmias can be caused by several factors, such as coronary artery disease, heart valve problems or hyperthyroidism.

ATHEROSCLEROSIS

A common disease in which deposits of plaque containing fatty substances, such as cholesterol, are formed within the inner layers of the arteries. A common name for it is "hardening of the arteries." Atherosclerosis is a progressive condition over decades, chiefly affecting the arteries of the heart, brain, and extremities. Its complications, such as coronary artery disease and strokes, are the major causes of death in the United States.

CANCER

Cancer is second only to cardiovascular disease as the leading cause of death in older people. The single greatest risk for most cancers is increasing age. The American Cancer Society estimates that nearly 1 million Americans were diagnosed as having cancer in 1988 and more than half of them were over age 65. Cancers most prevalent among older people are: COLON CANCER, which struck an estimated 105,000 persons in 1988 and proved fatal for 53,500, 94% of those diagnosed with colorectal cancer were over age 50; BREAST CANCER, with about 135,000 new cases diagnosed in 1988, 42,000 women died of the disease, the incidence in women age 50 and older has been increasing since 1950; LUNG CANCER, the leading cause of cancer deaths, incidence of lung cancer sharply increases after age 55, there were an estimated 152,000 new cases of lung cancer in the United States in 1988 and approximately 139,000 deaths; PROSTATE CANCER with an estimated 99,000 new cases and 28,000 deaths in 1988, about 80% of prostate cancers are diagnosed in men over 65; SKIN CANCER including the most serious type, malignant melanoma, which occurs in about 27,000 people annually and causes 5,800 deaths; and MOUTH CANCER, which was diagnosed in about 30,000 people in 1988 and killed more than 9,000.

CARDIOVASCULAR DISEASE

Cardiovascular diseases that commonly afflict older persons include arrhythmias, atherosclerosis, congestive heart failure, coronary artery disease, heart attack, high blood pressure, peripheral vascular disease, and stroke. Heart disease is the leading cause of death in the United States, particularly among older persons, and stroke ranks third. (See more on the individual diseases listed under their names.)

CONGESTIVE HEART FAILURE

The end result of many different types of heart disease. The heart cannot pump blood out normally. This results in congestion (water and salt retention) in the lungs, swelling in the extremities, and reduced blood flow to body tissues.

CORONARY ARTERY DISEASE

Caused by atherosclerosis of the arteries that supply the heart. Angina (decreased blood flow to the heart muscle) causes chest pain in the area of the heart. Heart attacks and congestive heart failure result from coronary artery disease. It is the most common cause of cardiovascular disability and death in the United States.

DEPRESSION

May result from a number of biologic, sociologic and psychologic factors associated with aging: decreasing mental and physical abilities, multiple medical problems, chronic pain, loss of independence, change in lifestyle such as retirement, death of friends and family members, children moving away, and economic insecurity. Early dementia and depression may be confused with one another. It is characterized by: loss of interest or pleasure in usual activities, sadness, feelings of hopelessness, irritability, poor appetite, insomnia, loss of energy, and lack of concentration. Suicidal thoughts may occur. Depression occurs in one-third of patients with Parkinson's disease and a substantial number of stroke victims. It is treatable using social support, psychotherapy and medication. About 8% of the 28.5 million people over 65 had symptoms of depression, according to 1985 estimates by the American Psychiatric Association. Many patients in nursing homes have psychiatric disorders, including depression, according to the association.

GLAUCOMA

An eye disease associated with increased pressure within the eyeball. If untreated, it may lead to permanent and complete blindness. Its onset is insidious in older age groups. There are no symptoms in early stages. Gradual loss of peripheral vision over a period of years eventually results in tunnel vision. 1–2% of people over 40 have glaucoma; about 25% of these cases are undetected. More than 1 million people over 65 in 1987 had glaucoma, according to the National Center for Health Statistics.

GOUT

A type of arthritis characterized by an excess of uric acid in the blood. Crystals of uric acid precipitate inside the joint cavity and set off an attack. Attacks occur suddenly, frequently at night, and often are accompanied by great pain. The feet, ankles, and knees are commonly affected, particularly the big toe. Proper drug treatment can quickly terminate the attack. About 95% of cases are in men. About 1 million Americans have gout, according to 1985 data from the Arthritis Foundation.

HEART ATTACK

A blood clot in an artery obstructs blood flow and can cause a part of the heart muscle to die due to oxygen deprivation. Sudden death may occur.

HIGH BLOOD PRESSURE

More than 60 million adults in the United States have hypertension. Without treatment, it greatly increases the incidence of cardiovascular disease, stroke and kidney failure. In about 95% of the cases, there is no known cause.

OSTEOARTHRITIS

A degenerative disease in which cartilage in the joints is worn away and reactive bony deposits form. It is the most common form of joint disease. According to 1985 data from the Arthritis Foundation, an estimated 15.8 million adults in the United States suffer from it. Incidence of the disease increases with age. It usually involves large weight-bearing joints such as those of the hip, knee and lumbar spine, and tends to occur in joints that are damaged by diseases such as rheumatoid arthritis, by trauma such as a fracture, by occupational overuse, or by neurologic disorders. Obesity may also play a role. In the late stages, joints may become deformed, motion is limited, and pain increases. It may require hip joint replacement. Spine involvement causes low back pain, which is the most common cause of loss of work among older people.

OSTEOPOROSIS

The most common metabolic bone disease in older people. It may be associated with other diseases such as rheumatoid arthritis or with the use of medication such as corticosterioids. A reduction in bone mass leads to fractures, especially of the vertebrae, hips, and wrists. 6–8 million white females suffer from it in the United States. 25% of all white females over age 70 eventually develop fractures, loss of height, or chronic back pain due to vertebral compression. Collapsed or compressed vertebrae produce "dowager's hump." Fractures can cause catastrophic deterioration in quality of life and staggering expenses. The cost of hip fractures alone may exceed $1 billion a year. Estrogen replacement therapy, calcium therapy, exercise, and other changes in lifestyle can play a role in prevention and treatment.

PARKINSON'S DISEASE

Chronic neurologic disease of unknown cause, characterized by tremors, rigidity, and an abnormal gait. There is an imbalance in the body of dopamine and acetylcholine, neurotransmitters normally present in the brain. Drug therapies may help restore this balance, but they may also cause serious side effects. Some patients with advanced disease develop dementia. It is one of the most common chronic neurological diseases of later life. The United Parkinson's Foundation estimates that the average age of onset is early sixties; 3–5% of the population over 65 has Parkinson's. The organization estimates that about 10% of Parkinson's patients go to nursing homes. In the late stages of the disease, patients cannot wash, dress, or feed themselves.

PERIPHERAL VASCULAR DISEASE

The obstruction of blood supply to the extremities, particularly the legs, caused by atherosclerosis.

RHEUMATOID ARTHRITIS

A chronic inflammatory disease of unknown cause. It chiefly affects the synovial membranes—thin linings—of the joints, primarily the small joints of the hands, wrists, and feet; can involve larger joints—the knees, ankles, and cervical spine. Symptoms include morning stiffness, joint swelling, and pain. Can eventually cause joint deformities. Incidence and prevalence of this disease increases with age. Female patients outnumber males almost 3:1. Rheumatoid arthritis peaks in males of age 60–69 and in females 50–59. More than 2 million people have rheumatoid arthritis, according to 1985 data from the Arthritis Foundation.

STROKE

Usually caused by atherosclerosis. A blood clot obstructs a major blood vessel of the brain. It results in death or serious brain damage, such as paralysis or loss of speech.

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IN DEVELOPMENT
NEW MEDICINES
FOR OLDER AMERICANS

Presented by the Pharmaceutical Manufacturers Association
In cooperation with the American Cancer Society

December 1988

65 Drugs in Development

Anti-Cancer Research Gaining Momentum, Survey Shows

Sixty-five cancer drugs that are now in development are targeted to treat cancers commonly associated with older persons—including breast, colon, lung, mouth, prostate and skin cancers.

These 65 medicines are being developed by 45 companies.

The figures indicate that a strong anti-cancer research and development effort is underway by the nation's pharmaceutical companies— an effort that is significantly enhanced by biotechnology research techniques.

At least 19 of these medicines—29 percent—are biotechnology-based drugs. Biotechnology has become important to anti-cancer research because it helps explain how cancers develop in the body and enables researchers to boost the body's immune system to fight cancers. An earlier PMA survey of biotechnology medicines in development found that approximately 50 percent—48 drugs—were targeted against cancers that afflict all ages.

It seems clear that anti-cancer research is gathering momentum, although I must stress that the therapeutic significance of these medicines will not be known until clinical studies are completed and evaluated.

PMA joins the American Cancer Society in hoping that this listing of drugs in clinical trials will encourage more patients to volunteer for these trials.

This cancer drug survey is part of a broader PMA effort to identify all the products that are being developed to treat the principal diseases of older Americans. We are attempting in these surveys to quantify the extensive private sector research against such diseases.

The first survey in our "New Medicines for Older Americans" series identified 87 drugs that are being developed by 47 companies for heart disease, stroke and hypertension.

Cancer
Second of a series
on
New Medicines
for Older Americans.

Cancer is second only to cardiovascular disease as the leading cause of death in older people. The American Cancer Society estimates that 985,000 Americans will be diagnosed as having cancer in 1988, and more than half of them will be over age 65. Nearly 60 percent of the 395,000 Americans who will die from cancer this year will be over age 65.

Among the findings in the survey:

- 14 of the 65 products are being tested for more than one indication, or use, resulting in 97 separate clinical test projects, each of which is listed in the chart.
- 25 products being tested are for unspecified forms of cancer (listed under "Other" in the chart).
- 20 drugs are being tested for colon cancer, which will strike an estimated 105,000 persons this year and prove fatal for 53,500; 94 percent of those diagnosed with colorectal cancer will be over age 50.
- 16 drugs are targeted to treat breast cancer. About 135,000 new cases of breast cancer will be diagnosed this year, and 42,000 women will die of the disease. Since 1950, the rate of death caused by breast cancer for women age 50 and older has been consistently increasing.
- 14 are intended to treat lung cancer. Lung cancer is the most common form of cancer in the United States and the leading cause of cancer deaths. The incidence of lung cancer sharply increases after age 55. There will be an estimated 152,000 new cases in the United States in 1988 and approximately 139,000 deaths.
- 10 medicines are in tests or awaiting approval for prostate cancer, with an estimated 99,000 new cases and 28,000 deaths in 1988. About 80 percent of prostate cancers are diagnosed in men over 65 years old.
- 11 drugs also are in tests or awaiting approval to treat skin cancers, including the most serious type, malignant melanoma, which occurs in about 27,000 people annually and causes 5,800 deaths.
- 1 product is intended to treat mouth (oral cavity) cancer, which will be diagnosed in about 30,000 people this year, killing 9,100.

The final survey in our series of "New Medicines for Older Americans" will identify medicines in development for arthritis, Alzheimer's and other diseases. This is scheduled for completion January 31.

Gerald J. Mossinghoff, *President*
Pharmaceutical Manufacturers Association

Cancer Products In Development

Breast Cancer

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Epirubicin	Adria (Columbus, OH)		application submitted
Toremifene	Adria (Columbus, OH)		Phase II/III
Elobromol Dibromodulcitol	Amswiss Pharmaceuticals, Inc. (San Antonio, TX)	(See also lung, skin)	Phase II
Granisetron 43694	Beecham Laboratories (Bristol, TN)	adjunct to chemotherapy (See also colon, lung, prostate)	Phase I
BMY 28090	Bristol-Myers (New York, NY)	(See also colon, lung, prostate)	Phase I/II
L-6 Monoclonal Antibody	Bristol-Myers (New York, NY)	(See also colon, lung, prostate)	Phase I
Paraplatin Carboplatin	Bristol-Myers (New York, NY)	(See also colon, lung, prostate)	Phase II/III
Proleukin Interleukin–2	Cetus (Emeryville, CA)	(See also colon, lung, skin)	Phase II
A.P.D. CGS 16949	Ciba-Geigy (Summit, NJ)		Phase III
LY186641 Sulfonylurea	Eli Lilly (Indianapolis, IN)	(See also colon, lung, prostate)	in clinical trials
LY188011 Difluorodeoxycytidine	Eli Lilly (Indianapolis, IN)	(See also colon, lung)	in clinical trials
LY264618	Eli Lilly (Indianapolis, IN)	(See also colon, lung)	in clinical trials
Fenretinide	McNeil Pharmaceutical (Spring House, PA)		Phase III
MDL 18,962	Merrell Dow (Cincinnati, OH)		Phase I
Tomosar SP Menogaril	Upjohn (Kalamazoo, MI)		Phase II
Liposomal Doxirubicin	Vestar (San Dimas, CA) Lyphomed, Inc. (Rosemont, IL)		Phase II

Colon Cancer

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Granisetron 43694	Beecham Laboratories (Bristol, TN)	adjunct to chemotherapy (See also breast, lung, prostate)	Phase I
BMY 28090	Bristol-Myers (New York, NY)	(See also breast, lung, prostate)	Phase I/II
L–6 Monoclonal Antibody	Bristol-Myers (New York, NY)	(See also breast, lung, prostate)	Phase I
Paraplatin Carboplatin	Bristol-Myers (New York, NY)	(See also breast, lung, prostate)	Phase II/III
Panorex MAb 17–1A	Centocor (Malvern, PA)		Phase II
Proleukin Interleukin–2	Cetus (Emeryville, CA)	(See also breast, lung, skin)	Phase II
CYT–103^{90}Y	CYTOGEN Corp. (Princeton, NJ)		Phase I

The content of this chart has been obtained through industry sources based on the latest information. Chart current as of December 1, 1988. The information may not be comprehensive. For more specific information about a particular product, contact the individual company directly. For general information, contact the Pharmaceutical Manufacturers Association at (202) 835-3463. *(If you did not receive your own copy of this issue of "Cancer Products in Development," please write to the Communications Division at the Pharmaceutical Manufacturers Association.)*

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Other *(drugs that have potential for one or more of the previous cancers; indications not yet determined)*

DRUG	COMPANY	INDICATIONS	U.S. DEVELOPMENT STATUS
Sterecyt Prednimustine	Pharmacia (Piscataway, NJ)		Phase II
Speratine™ Spiromustine	Roberts (Eatontown, NJ)		Phase II
Granulocyte Macrophage Colony Stimulating Factor (GM-CSF)	Schering-Plough (Madison, NJ) Sandoz (East Hanover, NJ) Genetics Institute (Cambridge, MA)	adjuvant to chemotherapy	Phase II/III
Carbetimer	G.D. Searle & Co. (Chicago, IL)		Phase II
Interleukin–4	Sterling Drug (New York, NY) Immunology Ventures (Seattle, WA)		Phase I
Liposomal Daunorubicin	Vestar (San Dimas, CA)		Phase I
AS101	Wyeth-Ayerst (Philadelphia, PA)		Phase II

GLOSSARY

Adjuvant/adjunct—A substance or drug that aids or helps another become effective or more effective. An adjunct also aids the delivery of a drug to a place where it is most effective in the body.

Application submitted—An application for marketing has been submitted by the company to the Food and Drug Administration (FDA).

Phase I—Safety testing and pharmacological profiling in humans.

Phase II—Effectiveness testing in humans.

Phase III—Extensive clinical trials in humans.

A Strong System is Needed to Recruit Participants for Clinical Testing of Cancer Drugs

by Gerald P. Murphy, M.D., Senior Vice President, Medical Affairs, American Cancer Society

This chart from the Pharmaceutical Manufacturers Association of anti-cancer drugs in clinical trials can help in at least two ways with a very tough problem—obtaining enough participants for cancer drug clinical trials.

1. *Doctors and patients are not sufficiently aware of what drugs are available and where they are being tested.* Information is the first step in getting people into advanced treatment programs. We have that information now in a readily accessible form.

This chart contains comprehensive information on cancer drugs in the clinical test phase, and the American Cancer Society will assist in getting it to oncologists and their patients.

2. *Some patients avoid clinical trials, because they are under the erroneous impression that the patient may end up in a control group and get a placebo instead of the experimental medicine.* Clearly, the patients and their physicians must thoroughly satisfy themselves concerning study design, but the fact is, current practice in cancer research involves the use of standard treatment as the control. That is, the new treatment is compared to the existing standard treatment, if there is one. The American Cancer Society advises that such trials be viewed as being consistent with the best medical care that an individual with cancer can receive.

We are confident that this chart, with its valuable information about drugs in development and their sources, can lead to greater trial participation by making it easier for physicians to inquire about the trials and by satisfying concerns about control group treatment.

It is apparent from the chart that research-based pharmaceutical companies are engaged in an enormous effort to develop promising new therapies for cancer. This list presents only a partial picture of therapies in development—only those that have progressed to clinical trial stage. Yet it is clear that the outlook for drug therapy has never been more promising.

The eventual delivery of these drugs from the laboratory to the patient depends greatly on the clinical test system to satisfy questions of safety and efficacy. This system cannot be permitted, through inadequate available participants, to become the weak link in speeding these drugs into widespread use.

Provided as a Public Service by the Pharmaceutical Manufacturers Association.

Pharmaceutical
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Colon Cancer

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Gamma Interferon	Genentech (S. San Francisco, CA)	(See also lung, skin)	Phase III
Macrophage Colony Stimulating Factor (M-CSF)	Genetics Institute (Cambridge, MA)	(See also skin, other)	Phase I
Monoclonal Antibody (NRCO–4)	Genetics Institute (Cambridge, MA) NeoRx (Seattle, WA)		Phase I
Leucovorin Calcium (w/5-fluorouracil)	Lederle (Wayne, NJ)		application submitted
LY186641 Sulfonylurea	Eli Lilly (Indianapolis, IN)	(See also breast, lung, prostate)	in clinical trials
LY188011 Difluorodeoxycytidine	Eli Lilly (Indianapolis, IN)	(See also breast, lung)	in clinical trials
LY264618	Eli Lilly (Indianapolis, IN)	(See also breast, lung)	in clinical trials
MDL 72,175	Merrell Dow (Cincinnati, OH)		Phase I
Colon RE–186	NeoRx (Seattle, WA)		Phase I
Tauricyt Tauromustine (TCNU)	Pharmacia (Piscataway, NJ)		Phase III
Ovamid™	Ribi ImmunoChem Research (Hamilton, MT)		Phase I
Spiro 32 Spirogermanium	Unimed (Somerville, NJ)		Phase II
XomaZyme®–Mel	Xoma (Berkeley, CA)	(See also skin)	Phase I

Lung Cancer

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Neupogen™ Granulocyte Colony Stimulating Factor	Amgen (Thousand Oaks, CA)	adjunct to enhance effect of chemotherapy	Phase III
Elobromol Dibromodulcitol	Amswiss Pharmaceuticals, Inc. (San Antonio, TX)	(See also breast, skin)	Phase II
Granisetron 43694	Beecham Laboratories (Bristol, TN)	adjunct to chemotherapy (See also breast, colon, prostate)	Phase I
BMY 28090	Bristol-Myers (New York, NY)	(See also breast, colon, prostate)	Phase I/II
L–6 Monoclonal Antibody	Bristol-Myers (New York, NY)	(See also breast, colon, prostate)	Phase I
Paraplatin Carboplatin	Bristol-Myers (New York, NY)	(See also breast, colon, prostate)	Phase II/III
Interleukin–2 with Tumor Necrosis Factor (TNF)	Cetus (Emeryville, CA)		Phase I/II
Proleukin Interleukin–2	Cetus (Emeryville, CA)	(See also breast, colon, skin)	Phase II
Gamma Interferon	Genentech (S. San Francisco, CA)	(See also colon, skin)	Phase III
LY186641 Sulfonylurea	Eli Lilly (Indianapolis, IN)	(See also breast, colon, prostate)	in clinical trials
LY188011 Difluorodeoxycytidine	Eli Lilly (Indianapolis, IN)	(See also breast, colon)	in clinical trials

Lung Cancer

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
LY264618	Eli Lilly (Indianapolis, IN)	(See also breast, colon)	in clinical trials
Radinyl® Etanidazole	Du Pont (Wilmington, DE) Roberts (Eatontown, NJ)	(See also mouth, other)	Phase II/III
CI-898 Trimetrexate	Warner-Lambert (Morris Plains, NJ)		Phase III

Mouth (oral cavity) Cancer

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Radinyl® Etanidazole	Du Pont (Wilmington, DE) Roberts (Eatontown, NJ)	(See also lung, other)	Phase II/III

Prostate Cancer

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Granisetron 43694	Beecham Laboratories (Bristol, TN)	adjunct to chemotherapy (See also breast, colon, lung)	Phase I
BMY 28090	Bristol-Myers (New York, NY)	(See also breast, colon, lung)	Phase I/II
L-6 Monoclonal Antibody	Bristol-Myers (New York, NY)	(See also breast, colon, lung)	Phase I
Paraplatin Carboplatin	Bristol-Myers (New York, NY)	(See also breast, colon, lung)	Phase II/III
Suprefact® Buserelin	Hoechst-Roussel (Somerville, NJ)		application submitted
Zoladex Goserelin Acetate	ICI Pharmaceuticals (Wilmington, DE)		application submitted
LY186641 Sulfonylurea	Eli Lilly (Indianapolis, IN)	(See also breast, colon, lung)	in clinical trials
Decapeptyl™	Organon, Inc. (West Orange, NJ)	(See also other)	Phase III
Eulexin® Flutamide	Schering-Plough (Madison, NJ)		application submitted
Lupron Leuprolide Acetate	TAP Pharmaceuticals (N. Chicago, IL)	for monthly injection	application submitted

Skin Cancer

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Elobromol Dibromodulcitol	Amswiss Pharmaceuticals, Inc. (San Antonio, TX)	(See also breast, lung)	Phase II
Proleukin Interleukin-2	Cetus (Emeryville, CA)	(See also breast, colon, lung)	Phase III
Actinex	Chemex (Denver, CO)		Phase II
Gamma Interferon	Genentech (S. San Francisco, CA)	(See also colon, lung)	Phase III
Macrophage Colony Stimulating Factor (M-CSF)	Genetics Institute (Cambridge, MA)	(See also colon, other)	Phase I
IL-2 Interleukin-2	Hoffmann-La Roche (Nutley, NJ)		Phase II/III
	Immunex (Seattle, WA)	in combination w/**Roferon®** -A	Phase II

Skin Cancer

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Roferon®–A Interferon alfa-2a	Hoffmann-La Roche (Nutley, NJ)		Phase II
RETIN–A® Tretinoin	Ortho Pharmaceutical (Raritan, NJ)		Phase III
Detox™	Ribi ImmunoChem Research (Hamilton, MT)		Phase II
Intron A Interferon-alpha2b	Schering-Plough (Madison, NJ)		application submitted
XomaZyme®–Mel	Xoma (Berkeley, CA)	(See also colon)	Phase II

Other *(drugs that have potential for one or more of the previous cancers; indications not yet determined)*

DRUG	COMPANY	INDICATIONS	U.S. DEVELOPMENT STATUS
BMY–25801	Bristol-Myers (New York, NY)	adjunct to chemotherapy	Phase II/III
BMY–28175	Bristol-Myers (New York, NY)		Phase I
Alkeran	Burroughs Wellcome (Research Triangle Park, NC)		Phase III
Piritrexim	Burroughs Wellcome (Research Triangle Park, NC)		Phase II
DuP–785	Du Pont (Wilmington, DE)		Phase II
Radinyl® Etanidazole	Du Pont (Wilmington, DE) Roberts (Eatontown, NJ)	(See also lung, mouth)	Phase II/III
Tumor Necrosis Factor (TNF)	Genentech (S. San Francisco, CA)		Phase II
Macrophage Colony Stimulating Factor (M-CSF)	Genetics Institute (Cambridge, MA)	(See also colon, skin)	Phase I
Granulocyte Macrophage Colony Stimulating Factor (GM-CSF)	Immunex (Seattle, WA) Behringwerke A.G. (subsidiary of Hoechst A.G. Marburg, W. Germany)		Phase II/III
Amonafide	Knoll Pharmaceuticals (Whippany, NJ)		Phase I
Tumor Necrosis Factor (TNF)	Knoll Pharmaceuticals (Whippany, NJ)		Phase I
Fazarabine	Lederle (Wayne, NJ)		Phase II
Platinum I	Lederle (Wayne, NJ)		Phase I
Platinum II	Lederle (Wayne, NJ)		Phase I
DOX 99 Doxorubicin Liposomal	The Liposome Company (Princeton, NJ)		Phase I
Plat 23	The Liposome Company (Princeton, NJ)		Phase I
Interleukin–2	Ortho Pharmaceutical (Raritan, NJ) Amgen (Thousand Oaks, CA)		in clinical trials
Decapeptyl™	Organon, Inc. (West Orange, NJ)	(See also prostate)	Phase II

IN DEVELOPMENT

NEW MEDICINES

FOR OLDER AMERICANS

Presented by the Pharmaceutical Manufacturers Association

October 1988

No. 1 Target of Research

Survey Finds 87 Drugs in Development for Cardiovascular Disease

Cardiovascular disease, the leading cause of death among older persons, has become the number one target for new drug research and development by the U.S. pharmaceutical industry.

A new survey by the Pharmaceutical Manufacturers Association shows 47 companies are developing 87 drugs for heart disease, hypertension and stroke, more than are being tested for any other disease.

Pharmaceutical companies spend the largest portion of their research and development investment—nearly 26 percent—on finding medicines for heart and circulatory disease, accounting for approximately $1.4 billion of the industry's $5.4 billion research and development budget in 1987.

The PMA survey of heart disease drugs in development is part of a series of surveys, "New Medicines for Older Americans," conducted by the association. The results show products in the industry's research pipeline that are targeted for diseases that primarily afflict older persons.

Details of the drugs in development for other aging diseases will be released by the PMA over a 4-month period in a series of charts.

All the drugs in this first chart in the series—Heart/Stroke/ Hypertension—are in human test stages or awaiting approval at the Food and Drug Administration.

30 of the 87 products are being tested for more than one indication, or use, resulting in 123 separate research and development projects. These are listed separately in the attached chart.

The most concentrated testing and development is for hypertension. Some 38 products are being tested for this use; all but 3 of them are in the final stages of development.

Heart Disease
Stroke
Hypertension
First of a series
on
New Medicines
for Older Americans.

Many products being tested for other cardiovascular diseases also are tested for hypertension because of its close association with other heart diseases. According to the Public Health Service, controlling high blood pressure can be one of the most effective means available of saving lives because hypertension can lead to heart disease and stroke.

The second most concentrated area of testing is congestive heart failure, the final and potentially fatal result of heart and vascular disease problems. There are 28 products in development for congestive heart failure, two-thirds of which are in advanced development stages.

There are 8 products in tests for arrhythmia, 9 for atherosclerosis, 17 for coronary artery disease/angina, 7 for heart attack and 8 for peripheral vascular disease.

Of the 6 products for stroke, 3 are versions of tissue plasminogen activator (tPA), which already is approved for treatment of heart attacks.

Heart disease is the leading cause of death in the United States, particularly among older persons, and stroke ranks third. Some 36 percent of all U.S. deaths are the result of heart disease and 7 percent are the result of stroke.

Although the death rate from cardiovascular disease has dropped 41 percent in the past 20 years from 363 to 213 per 100,000 population, the aging of the population is likely to result in increased incidence of cardiovascular disease.

I am pleased to release this list of the 87 new drug therapies that are being developed for heart and circulatory diseases by the nation's pharmaceutical industry.

New medicines for older Americans hold the promise of longer, better quality lives and also can result in shorter hospital stays, fewer operations, and continued independence for older persons. With the increasing numbers of older persons in our society, this clearly is one of our industry's most important challenges.

Gerald J. Mossinghoff, *President*
Pharmaceutical Manufacturers Association

Cardiovascular Products In Development

Arrhythmia

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
CK 1752 Sematilide	Berlex Laboratories (Wayne, NJ)		Phase II
Diprafenone	Berlex Laboratories (Wayne, NJ)		Phase II
Lopressor Metoprolol Tartrate	Ciba-Geigy (Summit, NJ)	(See also coronary artery disease/angina)	application submitted
Decabid Indecanide	Eli Lilly (Indianapolis, IN)		in human clinicals
Cipralan Cifenline	Hoffmann-La Roche (Nutley, NJ) Glaxo (Research Triangle Park, NC)		application submitted
Rythmol Propafenone	Knoll Pharmaceuticals (Whippany, NJ)		application submitted
Recainam	Wyeth-Ayerst (Radnor, PA)		Phase III
WY-48,986	Wyeth-Ayerst (Radnor, PA)		Phase I

Atherosclerosis

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
BMY 21891	Bristol-Myers (New York, NY)	(See also coronary artery disease)	Phase I
HWA 448 Torbafylline	Hoechst-Roussel (Somerville, NJ)	(See also peripheral vascular disease)	Phase II
15-Ketosterol	Lederle (Wayne, NJ)		Phase I
Nilvadipine (calcium channel blocker)	Lederle (Wayne, NJ)	(See also hypertension)	in human clinicals
TA 3090	Marion Laboratories (Kansas City, MO)	(See also coronary artery disease/angina, hypertension, peripheral vascular disease)	Phase I
DynaCirc Isradipine	Sandoz (East Hanover, NJ)	(See also hypertension)	Phase III
Pravachol Pravastatin	Squibb (Princeton, NJ)		application submitted
Cardene Nicardipine	Syntex (Palo Alto, CA)	(See also coronary artery disease/angina, hypertension, stroke)	Phase II
Ciprostene Calcium	Upjohn (Kalamazoo, MI)	(adjunct therapy for balloon angioplasty; see also peripheral vascular disease)	Phase II

Congestive Heart Failure

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Manoplax Flosequinan, BTS 49,465	The Boots Company (Lincolnshire, IL)	(See also hypertension)	Phase III

The content of this chart has been obtained through industry sources based on the latest information. Chart current as of October 15, 1988. The information may not be comprehensive. For more specific information about a particular product, contact the individual company directly. For general information, contact the Pharmaceutical Manufacturers Association at (202) 835-3463. *(If you did not receive your own copy of this issue of "New Medicines for Older Americans," please write to the Communications Division at the Pharmaceutical Manufacturers Association.)*

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Hypertension

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
DynaCirc Isradipine	Sandoz (East Hanover, NJ)	(See also atherosclerosis)	application submitted
Spirapril	Schering-Plough (Madison, NJ) Sandoz (East Hanover, PA)	(See also congestive heart failure)	Phase III
Unicard® Dilevalol	Schering-Plough (Madison, NJ)		application submitted
Carvedilol SK & F 105517	SmithKline Beckman (Philadelphia, PA)		Phase III
Corlopam Fenoldopam— SK & F 82526	SmithKline Beckman (Philadelphia, PA)	(See also congestive heart failure)	Phase III
Fosinopril	Squibb (Princeton, NJ)		Phase III completed
Zofenopril	Squibb (Princeton, NJ)	(See also congestive heart failure)	Phase III
Cardene Nicardipine	Syntex (Palo Alto, CA)	(See also atherosclerosis, coronary artery disease/angina, stroke)	application submitted
RS 93522	Syntex (Palo Alto, CA)	(See also congestive heart failure)	Phase I
CI-775 Bevantolol	Warner-Lambert (Morris Plains, NJ)		application submitted
CI-906 Quinapril Accupril	Warner-Lambert (Morris Plains, NJ)	(See also congestive heart failure)	Phase III

GLOSSARY

Adjunct—A substance or drug that aids or helps another drug to act.

Angina (pectoris)—A symptom of coronary artery disease. Narrowed coronary arteries result in decreased blood flow to the heart muscle typically causing chest pain in the area of the heart.

Application submitted—An application for marketing has been submitted by the company to the Food and Drug Administration (FDA).

Arrhythmia—Abnormal heart rhythm usually detected by an electrocardiogram. Arrhythmias can be caused by several factors, such as coronary artery disease, heart valve problems or hyperthyroidism.

Atherosclerosis—A common disease in which deposits of plaque containing fatty substances, like cholesterol, are formed within the inner layer of the arteries. A common name for it is "hardening of the arteries." Atherosclerosis is a progressive condition over decades, chiefly affecting the arteries of the heart, brain and extremities. Its complications, such as coronary artery disease and strokes, are the major causes of death in the United States.

Balloon angioplasty—A balloon catheter is inserted into a clogged or narrowed coronary artery to improve blood circulation by dilating the vessel, either by flattening plaque against the artery wall or by breaking up the plaque.

Cardiac glycoside intoxication—Cardiac glycoside is a drug that helps a failing heart to pump more strongly. Although cardiac glycosides, such as digoxin, are sometimes used in treating congestive heart failure, there is a fine line between their therapeutic and toxic levels. Too much digoxin, for instance, can cause anorexia, nausea and vomiting, headache, vision problems and disorientation. All of these symptoms can precede serious cardiac toxicity, which most often manifests itself as arrhythmias.

Congestive heart failure (CHF)—In CHF, the end result of many different types of heart disease, the heart cannot pump blood out normally. This results in congestion (water and salt retention) in the lungs, edema in the extremities and reduced blood flow to body tissues.

Coronary artery disease (CAD)—Atherosclerosis of the large and medium-sized arteries of the heart is the cause of most CAD. The major complications of CAD are angina pectoris, heart attacks and congestive heart failure. It is the most common cause of cardiovascular disability and death in the United States.

Edema—Abnormally large amounts of fluid build up in body tissues causing swelling.

Heart attack/coronary thrombosis/myocardial infarction—A coronary thrombosis is a blood clot in an artery of the heart that obstructs the blood flow and can cause sudden death. In myocardial infarction, a part of the heart muscle (myocardium) dies as a result of blood and oxygen deprivation.

Hypertension—More than 60 million adults in the United States have hypertension, also known as high blood pressure. Without treatment, it greatly increases the incidence of cardiovascular disease—coronary artery disease, heart attack, stroke and kidney failure. In about 95 percent of the cases, there is no known cause.

Peripheral vascular disease—The obstruction of blood supply to the extremities, particularly the legs, caused by atherosclerosis.

Phase I—Safety testing and pharmacological profiling in humans.

Phase II—Effectiveness testing in humans.

Phase III—Extensive clinical trials in humans.

Pulmonary embolism—A blood clot that obstructs the pulmonary artery, which transports blood from the heart to the lungs. More than 90 percent of pulmonary emboli originate as clots in the deep veins of the lower extremities. In some cases, they result in sudden death.

Stroke/cerebral thrombosis—Usually caused by atherosclerosis, a blood clot obstructs a major blood vessel of the brain, resulting in death or serious brain damage, such as paralysis or loss of speech.

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Congestive Heart Failure

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Bucindolol	Bristol-Myers (New York, NY)		Phase II
Auriculin Atrial Peptide	California Biotechnology (Mountain View, CA) Wyeth-Ayerst (Radnor, PA)		Phase II
Benazepril	Ciba-Geigy (Summit, NJ)	(See also hypertension)	Phase III
Indolidan	Eli Lilly (Indianapolis, IN)		in human clinicals
Isomazole	Eli Lilly (Indianapolis, IN)		in human clinicals
Dopacard Dopexamine Hydrochloride Solution	Fisons Corporation (Bedford, MA)		Phase III
Arlix Piretanide	Hoechst-Roussel (Somerville, NJ)	(Also for edema)	application submitted
Cardace® Ramipril	Hoechst-Roussel (Somerville, NJ)	(See also hypertension)	Phase III
Inhibace Cilazapril	Hoffmann-La Roche (Nutley, NJ) Glaxo (Research Triangle Park, NC)	(See also hypertension)	Phase III
Carwin Xamoterol	ICI Pharmaceuticals (Wilmington, DE)		Phase III
ICI 153-110	ICI Pharmaceuticals (Wilmington, DE)		Phase I
Perindopril	McNeil Pharmaceutical (Spring House, PA)	(See also hypertension)	Phase III
Plendil MK-218/ Felodipine	Merck Sharp & Dohme (West Point, PA) Astra Pharmaceutical (Westboro, MA)	(See also coronary artery disease/angina, hypertension)	Phase III
Perfan Enoximone	Merrell Dow (Cincinnati, OH)		Phase III
Piroximone MDL 19,205	Merrell Dow (Cincinnati, OH)		Phase II
ORF-22867	Ortho Pharmaceutical (Raritan, NJ)		Phase I
Celectol Celiprolol	Rorer Group (Fort Washington, PA)	(See also hypertension)	application submitted
RGW-2938	Rorer Group (Fort Washington, PA)		Phase II
Spirapril	Schering-Plough (Madison, NJ) Sandoz (East Hanover, NJ)	(See also hypertension)	Phase III
Corlopam Fenoldopam— SK & F 82526	SmithKline Beckman (Philadelphia, PA)	(See also hypertension)	Phase III
Zofenopril	Squibb (Princeton, NJ)	(See also hypertension)	Phase III
Medorinone	Sterling Drug (New York, NY)		Phase I
Milrinone	Sterling Drug (New York, NY)		Phase III

Congestive Heart Failure

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
RS 93522	Syntex (Palo Alto, CA)	(See also hypertension)	Phase I
Nicorandil	Upjohn (Kalamazoo, MI)	(See also coronary artery disease/angina)	Phase II
CI-906 Quinapril Accupril	Warner-Lambert (Morris Plains, NJ)	(See also hypertension)	Phase III
Anaritide Peptide with Vasomotor Activity	Wyeth-Ayerst (Radnor, PA)		Phase II

Coronary Artery Disease/Angina

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Abbokinase Urokinase	Abbott Labs (North Chicago, IL)	(See also peripheral vascular disease)	Phase II
Procardia® XL Nifedipine	Alza (Palo Alto, CA) Pfizer (New York, NY)	(For angina only; see also hypertension)	application submitted
Eminase	Beecham Laboratories (Bristol, TN)		application submitted
Carvedilol SKF-105517	Boehringer Mannheim (Rockville, MD) SmithKline Beckman (Philadelphia, PA)	(For angina only; see also hypertension)	Phase III
BMY 21891	Bristol-Myers (New York, NY)	(See also atherosclerosis)	Phase I
Lopressor Metoprolol Tartrate	Ciba-Geigy (Summit, NJ)	(See also arrhythmia)	application submitted
Bisoprolol Fumarate	Lederle (Wayne, NJ)	(For angina only; see also hypertension)	Phase III
TA 3090	Marion Laboratories (Kansas City, MO)	(See also atherosclerosis, hypertension, peripheral vascular disease)	Phase I
McN-5691	McNeil Pharmaceutical (Spring House, PA)	(For angina only; see also hypertension)	Phase II
Vascor® Bepridil	McNeil Pharmaceutical (Spring House, PA)		application submitted
Plendil MK-218/ Felodipine	Merck Sharp & Dohme (West Point, PA) Astra Pharmaceutical (Westboro, MA)	(For angina only; see also congestive heart failure, hypertension)	Phase III
Amlodipine	Pfizer (New York, NY)	(For angina only; see also hypertension)	application submitted
Sulotroban SK & F 95587	SmithKline Beckman (Philadelphia, PA)		Phase II
Cardene Nicardipine	Syntex (Palo Alto, CA)	(For angina only; see also atherosclerosis, hypertension, stroke)	Phase II
RS 43285	Syntex (Palo Alto, CA)	(For angina only)	Phase II
Nicorandil	Upjohn (Kalamazoo, MI)	(For angina only; see also congestive heart failure)	Phase II
Betridil	Wallace Laboratories (Cranbury, NJ) McNeil Pharmaceutical (Spring House, PA)	(For angina only)	Phase III

Peripheral Vascular Disease

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Abbokinase Urokinase	Abbott Labs (North Chicago, IL)	(See also coronary artery disease/angina)	application submitted
Mg EDTA	A.H. Robins (Richmond, VA)		Phase II
Iloprost	Berlex Laboratories (Wayne, NJ)		Phase II
HWA 448 Torbafylline	Hoechst-Roussel (Somerville, NJ)	(See also atherosclerosis)	Phase II
Sufrexal/ Ketanserin	Janssen Pharmaceutica (Piscataway, NJ)	(See also hypertension)	Phase II/III
TA 3090	Marion Laboratories (Kansas City, MO)	(See also atherosclerosis, coronary artery disease/angina, hypertension)	Phase I
Ciprostene Calcium	Upjohn (Kalamazoo, MI)	(See also atherosclerosis)	Phase II
Itazigrel	Upjohn (Kalamazoo, MI)		Phase II

Stroke (Cerebral Thrombosis)

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Prolysis (+PA)	Burroughs Wellcome (Research Triangle Park, NC)	(See also heart attack)	application submitted
Tissue Plasminogen Activator	Genetics Institute (Cambridge, MA) Wellcome Biotechnology (Beckenham, England)	(See also heart attack, other)	Phase II/III
Arvin Ancrod	Knoll Pharmaceuticals (Whippany, NJ)		Phase II
ORG 10172	Organon (West Orange, NJ)		Phase II
Cardene Nicardipine	Syntex (Palo Alto, CA)	(See also atherosclerosis, coronary artery disease/angina, hypertension)	Phase II
Ticlid Ticlopidine	Syntex (Palo Alto, CA)		Phase III

Other

DRUG	COMPANY	INDICATIONS	U.S. DEVELOPMENT STATUS
Digidote Digoxin Immune Fab-Ovine	Boehringer Mannheim (Rockville, MD)	life-threatening acute cardiac glycoside intoxication	application submitted
Tissue Plasminogen Activator	Genetics Institute (Cambridge, MA) Wellcome Biotechnology (Beckenham, England)	pulmonary embolism (See also heart attack, stroke)	application pending

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Heart Attack (Coronary Thrombosis; Myocardial Infarction)

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Tissue Plasminogen Activator	Biogen (Cambridge, MA) SmithKline Beckman (Philadelphia, PA)		Phase II
Superoxide Dismutase	Bio-technology General (New York, NY)		Phase II
BM-13.177 SKF-95587	Boehringer Mannheim (Rockville, MD) SmithKline Beckman (Philadelphia, PA)		Phase II
Prolysis (+PA)	Burroughs Wellcome (Research Triangle Park, NC)	(See also stroke)	application submitted
Centorex Anti-platelet MAb	Centocor (Malvern, PA)		Phase I
Prourokinase	Collaborative Research (Bedford, MA) Sandoz (East Hanover, NJ)		Phase II/III
Tissue Plasminogen Activator	Genetics Institute (Cambridge, MA) Wellcome Biotechnology (Beckenham, England)	(See also stroke, other)	Phase II/III

Hypertension

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Hytrin/Enduron Terazosin/ Methyclothiazide combination	Abbott Labs (North Chicago, IL)		Phase III
Bopindolol	A.H. Robins (Richmond, VA)		Phase III
Quanfacine	A.H. Robins (Richmond, VA)		Phase III
Minipress/ Prazosin XL	Alza (Palo Alto, CA) Pfizer (New York, NY)		application submitted
OROS Potassium Chloride for Potassium Supplementation	Alza (Palo Alto, CA)		application submitted
Procardia® XL Nifedipine	Alza (Palo Alto, CA) Pfizer (New York, NY)	(See also coronary artery disease/angina)	application submitted
Carvedilol SKF-105517	Boehringer Mannheim (Rockville, MD) SmithKline Beckman (Philadelphia, PA)	(See also coronary artery disease/angina)	Phase III

Hypertension

DRUG	COMPANY	OTHER INDICATIONS	U.S. DEVELOPMENT STATUS
Manoplax Flosequinan, BTS 49,465	The Boots Company (Lincolnshire, IL)	(See also congestive heart failure)	Phase III
Benazepril	Ciba-Geigy (Summit, NJ)	(See also congestive heart failure)	application submitted
Pindac Pinacidil	Eli Lilly (Indianapolis, IN)		application submitted
Kerlone	G.D. Searle and Company (Chicago, IL)		application submitted
Cardace® Ramipril	Hoechst-Roussel (Somerville, NJ)	(See also congestive heart failure)	Phase III
Symcor Tiamenidine HCl	Hoechst-Roussel (Somerville, NJ)		application submitted
Baypress Nitrendipine	Hoffmann-La Roche (Nutley, NJ) Miles Inc. (West Haven, CT)		application submitted
Inhibace Cilazapril	Hoffmann-La Roche (Nutley, NJ) Glaxo (Research Triangle Park, NC)	(See also congestive heart failure)	Phase III
Inhibace Cilazapril/HCTZ	Hoffmann-La Roche (Nutley, NJ) Glaxo (Research Triangle Park, NC)		Phase III
Sufrexal/ Ketanserin	Janssen Pharmaceutica (Piscataway, NJ)	(See also peripheral vascular disease)	Phase II/III
Bisoprolol Fumarate	Lederle (Wayne, NJ)	(See also coronary artery disease/angina)	Phase III
Nilvadipine (calcium channel blocker)	Lederle (Wayne, NJ)	(See also atherosclerosis)	in human clinicals
Cardizem SR Diltiazem HCl Sustained Release	Marion Laboratories (Kansas City, MO)		application submitted
TA 3090	Marion Laboratories (Kansas City, MO)	(See also atherosclerosis, coronary artery disease/angina, peripheral vascular disease)	Phase I
McN-5691	McNeil Pharmaceutical (Spring House, PA)	(See also coronary artery disease/angina)	Phase II
Perindopril	McNeil Pharmaceutical (Spring House, PA)	(See also congestive heart failure)	Phase III
Plendil MK-218/ Felodipine	Merck Sharp & Dohme (West Point, PA) Astra Pharmaceutical (Westboro, MA)	(See also congestive heart failure, coronary artery disease/angina)	Phase III
Amlodipine	Pfizer (New York, NY)	(See also coronary artery disease/angina)	application submitted
Cardura Doxazosin	Pfizer (New York, NY)		application submitted
Celectol Celiprolol	Rorer Group (Fort Washington, PA)	(See also congestive heart failure)	application submitted

The CHAIRMAN. Well, maybe you'll have a chance with a few of the questions here, Mr. Mossinghoff. I'll start off. Once again, we'll have the 3-minute rule, if we will have the timer placed on. We do thank you for you coming today, Mr. Mossinghoff. Many of your members that we invited did not. That is their prerogative. We issued no subpoenas.

Now, do you feel that Congress, philosophically, should have a role in doing what we're doing? Do we have a role in looking at the prices that our consumers and taxpayers are paying for prescription drugs, which are necessities of life?

Mr. MOSSINGHOFF. In some ways, Mr. Chairman, we welcome these hearings, because I think it will give us a chance to show what enormous benefit this declining share of the health-care dollar is. It started off in 1965 at about plus 12 percent and now it's down to about 6.8. And I don't think anyone seriously questions that that 6.8 percent of the health care dollar is the most cost-effective. If, by using one of these 1-C ACE Inhibitors, you're able to obviate $40,000 heart bypass surgery, you've done a lot for the system.[7] The drug budget might be a problem because that is expensive therapy, but for the system you've done an enormous benefit.

So I no way question your right to look into this, and as I say, in some ways we welcome this inquiry.

The CHAIRMAN. Some of your members I don't think welcome the inquiry, but that's their preorogative, and won't go into this.

Now, you mentioned two or three of the C drugs that had been classified C by the Food and Drug Administration, little or no use, that they moved ultimately up into the A category. Out of the 292 C-rated drugs, classified by Food and Drug, 1981 to 1988, how many of the C category drugs ultimately moved into the A category?

Mr. MOSSINGHOFF. Well, Mr. Chairman, they don't really move into the A category. The 1-A, 1-B, and 1-C designation is given at the beginning of the review process at FDA, and it controls the pace of that review process. For example, AIDS now is 1 double A, so it's faster than anything else. Once the drug is approved, the proof of the pudding here is in the eating, and the fact that Zantac, which is a H2 anti-ulcer drug, moved in the world medical system to number one, that was the real test. So it's not so much the movement—there is no movement in FDA. It's the fact that ACE Inhibitors, Calcium Channel Blockers, Zantac, all these drugs are clearly recognized by the medical system as being very, very significant breakthroughs. Now, FDA doesn't go back and recalibrate. After a drug is approved, they don't go back and say, "Well we should have made that ACE Inhibitor a 1-A."

The CHAIRMAN. Well, I'm going to come back to that, but I'm going to do one final question.

How do you explain an 88 percent rise in drug price inflation versus the 28 percent general price inflation since 1981?

Mr. MOSSINGHOFF. Mr. Chairman, in my statement I point out several of the factors that have to do with that. One of the key factors is the fact that the market for brand name drugs virtually collapses, after the expiration of the patent, because of the Drug Price Competition and Patent Term Restoration Act of 1984. Beginning in 1984, our companies lost a major market share of the brand name drug to the generics. That's one of the forces. The delays at FDA in approving new drugs is another force. And the fact is that Act, which was passed by Congress in 1984, before I was at PMA, is like a two-act play. The first part of it, the economic effects of generic competition, are being felt. The second half, which is patent-term restoration, is only now beginning to be felt. Only 5 of the 61 patents on which the terms have been extended would be off patent at this point.

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[7] Committee staff note: In fact, "ACE inhibitors" are not used to obviate heart bypass surgery, according to Thomas Graboys, M.D., of Harvard University, one of the foremost experts on medical management as an alternative to heart bypass surgery.

The CHAIRMAN. Later on I'm going to show you a graph [8] that I hope is correct that shows that when a patent expires after 17 years and a generic or generics come on the market in competition that the patented drug, the formerly patented drug, the brand name drug, still rises in price commensurate with the 8, 9, or 10 percent per year.

Now, let's see. I don't know who is next. Senator Cohen, would you like to——

Senator COHEN. Well, just to follow up on that point, I mean, how extensive is the use of generics, Mr. Mossinghoff?

Mr. MOSSINGHOFF. As I understand the last survey, about 40 percent of the prescriptions filled in the United States are filled with generic drugs.

Senator COHEN. Well, how do you account for the Chairman's chart which will be forthcoming, that shows that continued rise in the costs of the patented drug even after the patent has expired compared to this penetration? I think you said, just repeated your statement that the market for brand name drugs collapses once the patent has expired. If that's the case, how would you have a patented drug, or prescription drug, nongeneric, continue to rise on the marketplace?

Mr. MOSSINGHOFF. Well, the volume of the market drops, relatively. The numbers I've seen are 50 percent in the first 2 years that a product is off patent. The pricing strategies, Senator, I really have to stay away from. PMA does not get involved. I'm sure there are companies that reduce the price after the patent expires, and obviously, there is no question there are companies that raise the price. But PMA cannot, does not, get involved in that strategy.

Senator COHEN. If they raise prices would that indicate there's still a market for it?

Mr. MOSSINGHOFF. Well, I think there's still a market, but the volume of the market drops significantly for most brand name drugs after the patent expires.

Senator COHEN. Would that mean that the price increase, then, is designed to compensate for the drop in the volume?

Mr. MOSSINGHOFF. I could only speculate, since we don't get involved, that that's part of the pricing strategy of our individual companies.

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[8] See appendix 1, p. 345.

Senator **Cohen**. Do your member companies themselves manufacture and sell generic drugs?

Mr. **Mossinghoff**. Yes, they do.

Senator **Cohen**. And what sort of bottom line do they have as far as a component of your member companies' operation—how big a component is it of those companies?

Mr. **Mossinghoff**. I don't know that answer, Senator. I don't know if PMA has that breakout or not. I think that a round number is that PMA companies probably supply about half of the generics sold in the United States, if that's helpful to you. I will attempt to get the other for the record, but I don't know the answer.

[Subsequent to the hearing, the following information was received for the record:]

Question. What percentage of the generic market is held by PMA companies?

Answer. To determine the share of the mulitiple-source market held by PMA companies, PMA compiled market-research data from IMS America on the top 26 multiple-source products. PMA restricted its analysis to those products and dosage forms for which FDA has judged generic competitors as bioequivalent. For two of the original 26 multiple-source products, there are no bioequivalent versions currently approved for marketing.

Based on the remaining 24 drugs, PMA estimates that PMA members, including the originator of the brand version, account for about 60 percent of both the prescriptions and the units (tablets or capsules) for these drugs. The originator brand alone represents about 50 percent of the prescriptions and units. For the generic market—i.e., the portion of the market that does not include the originator brand—PMA members account for about 25 percent of both the prescriptions and units.

Senator **Cohen**. That's all I have right now, Mr. Chairman.

The **Chairman**. Thank you, Senator Cohen.

Senator Warner.

Senator **Warner**. Thank you for the offer to come in here and help today, because I do believe within your industry we can get these answers. The absence, perhaps, of some of your members today—I think you can speak for them having had an opportunity to visit with you, and maybe at a subsequent hearing they can come in and individually, after we frame the bigger picture, contribute their knowledge. I would hope that would be the case, because right now there is this appearance that there is some gouging and that perhaps the member companies are hiding. But I don't think that's the case. Are they?

Mr. **Mossinghoff**. They're not gouging, Mr. Chairman.

Senator **Warner**. Are they hiding?

Mr. **Mossinghoff**. No, they're not hiding either. I really believe there was a genuine concern about discussion of proprietary information here.

Senator **Warner**. This chart, you saw the flat, basic return to the druggists, whereas the prices have gone up. Is there a reason for that?

Mr. **Mossinghoff**. Well, the price increase, as I indicated, has to do with a number of factors. The time during which the product life cycle exists, the United States has chosen as a policy to use generic substitution as a cost-control mechanism. That decision was made in 1984. Most of the European countries do not permit pharmacists to substitute generic products. They've chosen other ways. France has a very tight price regulation. The United Kingdom controls profits in some way or another. So there is a mixed bag of how one would control prices, and I would say that it's the forces, the delays in the FDA, plus the enormous R&D expenditure, and no one can deny that.

Senator WARNER. Let me go to another one. In your prepared statement you mentioned that the so-called average wholesale price is, not really an accurate standard of what pharmacists actually pay for drugs. And this is what I was trying to get at. Why isn't it, and is there a better standard to use?

Mr. MOSSINGHOFF. Well, the average wholesale price is not determined by our companies. It's determined in part from surveys done of our companies. It's also done by other surveys, as I think testimony today would indicate. The Inspector General of HHS did a report, and I believe it was in 1986, that showed that in general "average wholesale price," the price published in the literature, is about 16 percent higher than the price that pharmacists actually pay for the products. In response to that while the Medicare bill was pending, PMA suggested that the Secretary of HHS do actual bi-annual surveys to determine what the real wholesale price is, rather than relying on these published prices which are, I think everyone agrees, higher than the actual price that pharmacists pay.

Senator WARNER. You heard my questions to the previous panel about the marketplace and why the forces of competition aren't bringing a stronger pressure to adjust these prices downward. Is there a uniqueness to this market, different than, say, other commodities that our society has?

Mr. MOSSINGHOFF. I think there is, Senator. It's a unique situation. I think, among other things, the percentage of R&D is totally unique in the United States and the amount of R&D——

Senator WARNER. To the credit of the industry that they're putting in.

Mr. MOSSINGHOFF. That's right. And it is a highly competitive market. As an example, I cite Tagamet, which was the forerunner, and in fact the Nobel Prize was given to the discoverer of Tagamet, an anti-ulcer drug. You couldn't tell the manufacturer that makes it that there's no competition, because Zantac, Pepcid, and Axid are all on the market and they're all anti-ulcer drugs. Now, it may be that for a given patient your doctor would say that the Tagamet is the right one, or Zantac is the right one, there are differences in these, but it is an enormously competitive market, in many ways a very diffuse market, very unique.

Senator WARNER. My time is up, I see.

The CHAIRMAN. Yes. Senator Kohl.

By the way, I passed by Senator Kohl a moment ago and I apologize. It was your turn, Senator Kohl.

Senator KOHL. No problem.

Mr. Mossinghoff, I'd just like to establish some of the profit and return on investment figures in your industry. According to my information, your industry is running a rate of profit at around 14.5 percent of sales, and about 29.5 percent return on investment? Is that somewhere close?

Mr. MOSSINGHOFF. I have the Fortune magazine report which is as good as anything PMA has. That says that in terms of return on sales in 1988, it was 13.5, in terms of return on assets it was 13.1, in terms of return to stockholder's equity it was 23.6——

Senator KOHL. In 19 what?

Mr. MOSSINGHOFF. This is 1988. It was the one published, I guess, in the April issue——

Senator KOHL. Well, that's not much different from the numbers that I'm using. I would simply like to suggest that in American industry those are very, very good numbers, unusually high, toward the highest, not very many industries do better. All of those statements you would agree with?

Mr. MOSSINGHOFF. Well, on return to investors, which is really the key, we are 16th among American industries, well below tobacco, toys, and other things.

Senator KOHL. Sixteenth out of how many?

Mr. MOSSINGHOFF. Well, this is 16th, absolutely. We're number 16 in terms of return to investors.

Senator KOHL. Well, that's a pretty good number. I'm just suggesting that your industry does extremely well and it's not that they don't deserve to do well. I mean that's not where I'm—but we're certainly not in a situation here when we're talking about an industry that has so many problems, that are up against so many difficulties that they're in any danger for any reason of falling off a cliff and doing badly. They do extremely well.

Mr. MOSSINGHOFF. Well——

Senator KOHL. They are an investor's favorite.

Mr. MOSSINGHOFF. Well, the low rank of ours on total return to shareholders is noted, obviously, on Wall Street. Being 16th, that's a very high-risk industry, I think as you would appreciate.

Senator KOHL. Your price earnings, your PE ratio, which is another hallmark of investor interest, is very high.

Mr. MOSSINGHOFF. Yes.

Senator KOHL. Higher than tobacco companies.

Mr. MOSSINGHOFF. I don't know that. I'll defer, obviously.

Senator KOHL. Yes.

Any comment on my question to the other panel about the cost of Nitro Dur all the way from 1 cent at the hospital level to $30 at the retail level? Is there any comment?

Mr. MOSSINGHOFF. Well, Senator, I've heard the same. We really walk a wide ring around how our companies establish their pricing policy. We really have to as someone who receives their information on R&D and so on, we really have to keep a wide path between us and pricing policies. The testimony this morning sounded reasonable to me, but I am in no way independently able to corroborate it. Namely, it seemed to me that one cent was in effect a donation to the hospitals. I mean, I think you'd agree with that just objectively. But I don't have a basis and can't have a basis for responding, and I'm sorry.

Senator KOHL. I hope—my final observation—that one of the results of these hearings is that both the industry and the Government and all parties concerned can find a way to have a win/win situation where everybody is reasonably well satisfied. And I'm sure that's a great concern of yours, and I mean that sincerely, that everybody is reasonably well satisfied that the correct forces are working in a proper manner, because otherwise unhappy things happen to everybody. And you don't want that, and certainly no other party wants that. And there are, as you can tell, some concerns about how the process is working.

Mr. Mossinghoff. I understand, Senator.

The Chairman. Thank you, Senator Kohl.

Senator Kassebaum.

Senator Kassebaum. Mr. Mossinghoff, I'd be curious what your opinion is of why the pharmaceutical companies are not wishing to participate in the bidding out system that the Kansas Medicaid is trying?

Mr. Mossinghoff. Well, I can answer part of that. And I don't want to be oblique, but I really don't know. And PMA, as you understand, cannot get involved in whether they do or don't. That's an individual corporate decision, and competitors can't decide whether they're going to bid or not on a given program, collectively. They have to make the decision independently. PMA works very hard to rule out formularies. And indeed, we were successful last year in the pendency of the Catastrophic Act, to rule out formularies, which is generally recognized as being second-class medicine.

It means that if there are four drugs in a given category, and your doctor wants to give you Drug C, but Drug A is the only one on the formulary, that's what you're going to get or you'll pay for it yourself. And we were delighted to be able to convince Congress that a formulary is not a good approach. I believe that in the Kansas system, although our State people handle that, obviously, more directly than I, they do set up formularies. And we are institutionally opposed to that as being a way to keep needed pharmaceuticals, diverse pharmaceuticals, out of the hands of the people that need them.

Senator Kassebaum. In the question of the marketplace, are there any figures that show what percentage of the drugs are covered under third party providers? Do you know?

Mr. Mossinghoff. I think—I apologize—there are numbers, and I would attempt to provide those for the record and send them directly to you, but I can't answer that question this morning.

[Subsequent to the hearing, the following information was received for the record:]

Question. In the question of the marketplace, are there any figures that show what percentage of the drugs are covered under third-party providers?

Answer. The most recent source available for this data is the "Report on 1987 National Health Expenditures" prepared by the Health Care Financing Administration. This report provides an estimate of outpatient spending for drugs and medical sundries as well as the percentage of this spending paid for by public and private third parties. According to the HCFA actuaries, about 61 percent of spending in this category is attributable to prescription drugs.

HCFA estimates that, in 1987, 25 percent of the total expenditures for drugs and medical sundries was paid for by third parties. Assuming that none of the non-prescription component of the drugs and medical sundries category is paid for by third parties, about 41 percent of prescription expenses were paid by third parties. In 1977, according to the National Medical Care Expenditures Survey, only 25 percent of prescription expenses were paid by third parties.

Senator Kassebaum. Thank you.

Now, I'd like to ask you about the approach tried in Canada. Most of the highest priced drugs in the United States are those that are under patent protection—and I can fully understand and appreciate the need for that patent protection. In Canada, as I understand it, there has been what is called a mandated licensing system, where the drug manufacturer is required to lease out to producers manufacturing the drug in return for royalties paid back to the developer. What is your assessment of such a system?

Mr. **Mossinghoff**. Senator, you're right. There used to be compulsory patent licensing in Canada. They enacted it in 1969. Last year they turned away from what we think was a very mistaken public policy and enacted what was called C–22. And that bill restored the rights of a patentee to a market share in lieu of this extremely low 4 percent royalty. So that was done. We regard that in the pharmaceutical industry as an important first step to bringing their system into harmony with all the other developed countries' systems in the world.

Senator **Kassebaum**. So the Canadian system really wasn't working?

Mr. **Mossinghoff**. Not at all. The research was drastically cut. And we can provide this for the record, but I believe it's true that in the last decade Canada has not produced any new drugs, or at least any new chemical entities. The data I have indicate that they now plow back about 7 percent of sales in R&D, and it's their goal under this new legislation, C–22, to get to 10 percent by 1996. That's still significantly less than the 16 percent that we invest in the United States. And so, I think there was a recognition, and the reason they enacted C–22 was I think a self-serving recognition on their part, that they would have squeezed the industry so hard that the industry, in effect, was nonproductive. It couldn't exist under those circumstances. I think even though C–22, as I say, is not up to the standard of the United States, Germany, the UK, and the European Patent System, it's an important first step, and we hope to work with them to improve their intellectual property protection even more.

[Subsequent to the hearing, the following information was received for the record:]

Question. How many new chemical entities have originated in Canada in the last decade?

Answer. According to the "Drug Product Index" (Vol. 1, 1988), published by Paul de Haen International, Inc., three new chemical entities have originated in Canada since that country adopted a system of compulsory licensing of pharmaceutical patents in 1969. The new chemicals—all of which were developed by Merck Frosst Canada Inc.—and the year they were first marketed are: Blocadren (1973), Flexeril (1979) and Technetium TC-99 (1980).

Senator **Kassebaum**. Thank you, Mr. Chairman.

The **Chairman**. Thank you, Senator Kassebaum.

Senator Cohen.

Senator **Cohen**. I have one more question.

Mr. Mossinghoff, the PMA lobbied very hard during the debate on catastrophic health care to prevent drug benefits from being included. And I might say that some of the tactics were resented by a number of members on the Hill because there were misrepresentations made. But I was wondering about what the underlying philosophy behind it was. Was it the notion that once something is included as a benefit, it necessarily will follow that there will be an attempt to put limits on the costs?

Mr. MOSSINGHOFF. Senator, I really welcome that question. First, PMA did not lobby to keep the drug benefit out of the bill. We lobbied against the House-passed bill. Our concerns today are about whether the drug benefit, just the technology of the drug benefit, can come into play by January 1, 1991. The House-passed bill would have brought that benefit into effect 7 months ago. It would have gone into effect at the first of this year. The House-passed bill would have been hopelessly underfunded, and that was the thrust of the PMA lobbying effort. And I would be happy to talk to you sometime at greater length about misrepresentations, because we had a very high quality control, and I think that we can stand up to everything we said in the lobbying effort.

But nevertheless, to set the record straight——

Senator COHEN. Well, there were letters coming from people who never signed those letters, or agreed to sign letters that became the subject of some controversy.

Mr. MOSSINGHOFF. And I understand there was a controversy with respect to your State, and I would apologize for that, the misunderstanding. But in any event, we did not lobby against the drug benefit, we lobbied against the House-passed bill, which we thought would have been hopelessly underfunded going in right from the start, and even not implementable by the Federal Government. We worked very hard with the Senate Finance Committee and, indeed, endorsed the drug portion. We took no position on the catastrophic portion. We endorsed the drug portion of the Senate-passed bill, and we worked even harder in the conference to make sure that the Senate principles, which we thought were very responsive and responsible, found their way into the final Act, which they did.

Senator COHEN. Does PMA support the continuation of the prescription drug coverage in the catastrophic health bill?

Mr. MOSSINGHOFF. Well, we continue to support a financially sound drug benefit in the Catastrophic Act.

Now——

Senator COHEN. Do you think the bill as it is written today is financially sound?

Mr. MOSSINGHOFF. Well, I've read the most recent reports of the Congressional Budget Office, and it casts serious doubts on whether that is a financially sound bill. We haven't brought that to our board of directors, but PMA supports a financially sound, conservative drug benefit in the Medicare bill.

Senator COHEN. Thank you; Mr. Chairman.

The CHAIRMAN. Thank you, Senator Cohen.

Senator Heinz, who is the vice chair of this committee, of course, has been called to a markup of the Banking, S&L bill, I guess we'll call it, so we'll probably never see him again, period, ever. [Laughter.]

We'll just wave goodbye to John Heinz. But first, he wanted for me to apologize to you, Mr. Mossinghoff, and all the witnesses, and to the committee, for not being able to be here. He's also expressed to me his concern about some of the things that we're talking about today. He wanted me to ask this question. This is Senator Heinz' question: Like physicians, manufacturers are being called on to take a hard look at their role in reducing rising health-care costs. The physician community which is equally, if not more heterogeneous than manufacturers, has come to the table around payment reform and the development of practice guidelines. Question: If a hearing such as this is not the forum for an exchange of ideas, what other forum is there, and what areas of drug reimbursement and pricing might we find some middle ground? That's Senator Heinz' question.

Mr. MOSSINGHOFF. Well, I would think any of our CEO's would welcome the opportunity to meet confidentially and privately with the leadership of this committee to discuss their proprietary information, under appropriate confidential pledges. The materials that were asked of them go to the very heart of their marketing strategy. The answers are unknown to us at PMA, and indeed have to be unknown to us, and it's not one company. It's company A versus company B versus company C in a very, very competitive environment. The board members of the PMA that I talked to about this hearing had a very genuine concern about a public hearing, and masking a drug, for example, masking Pfizer's anti-arthritis drug, wouldn't mask it from anyone. I don't care what you call it—Drug A or Drug B—the market is very well understood by each of our companies, the entire market.

So, I suspect that might be something that would be appropriate. Another concern is that it's an extremely complicated, in effect, delicately balanced industry, the R&D expenditures and all the rest. And I think they'd welcome you or any other Committee member to their place and actually witness what goes into the development of a new drug.

The CHAIRMAN. If I saw it, I'm not sure I would know what I was seeing. I appreciate that, Mr. Mossinghoff.

Now, you talk about confidentiality and pricing mechanisms, and that the companies did not want to talk about prices, and they'd meet in confidence, et cetera. In the U.S. Government, in the Department of Commerce, Food and Drug Administration, anywhere else, do your members have to file the pricing mechanisms and the prices of the drugs they produce?

Mr. MOSSINGHOFF. Not to my knowledge, Mr. Chairman.

The CHAIRMAN. What about Canada? Does the Canadian Government require this?

Mr. MOSSINGHOFF. Under this C–22 legislation, there is a requirement that price comparisons with other countries be submitted to——

The CHAIRMAN. Would you object if we had a similar regulation or law on our books in this country to require this type of information?

Mr. MOSSINGHOFF. I really don't know how to answer that. I haven't brought that to the board. I don't think we would be anxious to see the Government getting itself involved in the free market. One of the hallmarks of the Medicare legislation was that you would rely upon the market to provide the checks and balances.

The CHAIRMAN. Mr. Mossinghoff, the situation is this, the Government is one of the major customers that your industry has. Furthermore, the Government, Medicare, is paying some of the highest prices of anyone, much higher than, for example, hospitals are paying, in fact sometimes several times more. We know nothing about the comparative prices. You refuse and your members refuse to come here to tell us how these price mechanisms work. How else are we to find out about it?

Mr. MOSSINGHOFF. Mr. Chairman, my first recommendation would be to discuss it in some confidential forum with the people involved, and in sufficient length so that an appreciation could be gotten, not under a 5-minute rule, because I would submit that there's no way the complicated forces could be explained in any intelligible way in 5 minutes, or even in a hearing in a morning.

The CHAIRMAN. Well, as more and more Senators leave, we're going to expand that rule from 5 minutes, or 3 minutes, a little further.

Senator Warner.

Senator WARNER. Well, let me just pick up on that. That's the unique way for us to conduct business, but I certainly, for one, am willing to explore the opportunity. How would you suggest, do we just sit in an informal—is this to protect the proprietary interests, or——

Mr. MOSSINGHOFF. I really believe the protection that—as you characterize it, the confidential forum would give—this one does not——

Senator WARNER. Other than maybe the short, brief 5-minute rule, or something?

Mr. MOSSINGHOFF. I think protection of confidentiality. Some of the questions asked by the Chairman go right to the heart of competitive pricing strategies. It's the most delicate of proprietary information. And in an open forum—there was a proposal, I think made in good faith by the committee and its staff, to mask drugs, instead of calling them by their names, calling them Drug A or Drug B. I would submit that it would take someone from a marketing staff about 30 milliseconds to know what drug you're talking about, and what the information concerns.

Senator WARNER. Well, now let's explore a little bit more. How would you like to go about it? And I certainly will entertain it. And perhaps other members of the committee likewise will do it.

Mr. MOSSINGHOFF. Well, I'm really not——

Senator WARNER. Let's just structure. What sort of a meeting and how would you like to go about it?

Mr. MOSSINGHOFF. The first thing I'd like to do, maybe, is discuss it with my executive committee, because I think I'm getting way out ahead of the board of directors.

The second thing, I would submit that I don't think any of our board members would be reluctant to come individually and talk at some length to the Committee in an executive session. However, I can't commit for the board, because it's obviously not something that the board has considered.

Senator WARNER. But I think it's important that we try and explore it together because, as I said in my brief opening statement, the problem is clear. The segment of the society least able to pay is burdened with these high costs. While it may well be clear, we're searching to try and find the answer. And I think that this industry, which is a very responsible industry, could help us in that search. And I, for one, say that if it's a confidential forum informally that can crack this problem, let's take a look at it. And I will explore it.

Mr. **MOSSINGHOFF**. I will specifically bring it to our executive committee.

Senator **WARNER**. And would you come back to me?

Mr. **MOSSINGHOFF**. I'll attempt to answer the question and come back to you, Senator.

Senator **WARNER**. Would you come back to me, or other members of the committee, whatever the case may be, the Chairman or otherwise? I expressed to you a willingness to sit down in a confidential forum and try and see what we can do to——

Mr. **MOSSINGHOFF**. I appreciate that very much and I think our board would appreciate that.

Senator **WARNER**. We'll do that.

Senator Cohen, my time is out. Did you want to follow on?

Senator **COHEN**. One question.

The importance of doing this, Mr. Mossinghoff, the chest pain drug, Transderm Nitroglycerin, that's available—my understanding is that it is available to hospitals for 1 cent per unit, even though at a pharmacy it costs some $32 per unit. Now, this rather, I would say, drastic discount not only gets physicians and interns used to using this particular drug, but more importantly it introduces patients to this particular drug. Now, is that a marketing strategy?

Mr. **MOSSINGHOFF**. Again, I would say—and both my common sense and my knowledge of the industry tell me—yes. I know that because our marketing people have told me that. But it sounds to me like it's not really a 1-cent sale, but that the companies are giving it to the hospital free, is the way I would characterize it. And that makes sense to me, but I really am not in a position to answer whether that's their marketing strategy or not, because they really don't get into that in PMA. That's an area of taboo for our trade association of competitors.

Senator **COHEN**. Well, I think that example is probably a good reason why Senator Warner's suggestion is imperative that we sit down as soon as possible to try and explore some of these questions.

Senator **WARNER**. Thank you.

The **CHAIRMAN**. How many manufacturers of pharmaceuticals do you have in the PMA, Mr. Mossinghoff?

Mr. **MOSSINGHOFF**. Well over 100, Mr. Chairman.

The **CHAIRMAN**. Well over 100 companies. Now, what I understand with discussions we've had with some of those companies, and also the responses to our invitations for them to come was that they evidently—and maybe I'm reading between the lines; tell me if I'm wrong—they think the Government ought to keep hands off. Is that what they think?

Mr. **MOSSINGHOFF**. I wouldn't characterize it that way at all, Mr. Chairman.

The **CHAIRMAN**. How would you characterize it?

Mr. **MOSSINGHOFF**. I would say that a hallmark of the legislation which PMA supported in the Senate and which we supported after it came out of conference was that you would rely on marketplace systems to deliver these drugs. This is not a single depot. You don't just deliver the drugs, you use the whole system. There are two parts to the VA system. The non-depot part of that system completely cuts out the pharmacists—the local pharmacist is not at all involved. The shipments go directly from the manufacturer to the VA under a negotiated schedule. That's a Government procurement system. The hallmark of the Medicare legislation was that you would rely upon the free-market forces, and, in fact, included in the legislation is the fact that discounts of pharmacists, those that are able to get discounts, should not be considered in deciding the reimbursement.

The CHAIRMAN. All right, Mr. Mossinghoff.

Our Government has, in fact, relied on the marketplace system or the free market system since 1981. We have seen an 88 percent increase in drug prices. How do we explain that to our constituents? I come from a State, for example, that has an over 65 elderly population percentage, ranked fifth in the United States. How do I go back home and tell them that I'm looking after their interests when your organization says hands off the marketplace, free enterprise, and I point to that chart and say, look, your drugs have increased 88 percent? And for you to exist, for you to live, you're going to be paying 88 percent more than you paid in 1981, and profits of the companies are at an all time high? How do I explain that?

Mr. MOSSINGHOFF. Well, I would start by explaining it, and I wish I had brought some charts—I wish I had brought some of the figures from my statement. But I'd start by explaining to them that from 1965 to the present, the expenditure for pharmaceuticals have drastically sloped down from over 12 to about 6.8 percent of total health-care expenditure. You've got to look at the whole health-care system. If you spent a lot of money on an ACE Inhibitor or a Calcium Channel Blocker, and that keeps your constituent out of the hospital for a $40,000 by-pass operation, that's money well spent. And I would explain also that drugs today are cheaper, they cost less than they did in 1967, when the 1967 Consumer Price Index was set at 100. The numbers are that if from 1967 until now were under a 1967 standard, would be about 370, we'd be about 350 and the rest of health care would be 520 plus. And so there are a lot of very good explanations for this most cost-effective slice of the health-care dollar.

The CHAIRMAN. Senator Warner, Senator Cohen, I apologize. I'm going to extend this a little bit, and then we'll have some extensions on both sides.

Now you say that drug prices have gone down?

Mr. MOSSINGHOFF. I'm saying that drug prices today are cheaper than they were in 1967.

The CHAIRMAN. For the same drugs?

Mr. MOSSINGHOFF. For the same basket of drugs.

The CHAIRMAN. What do you mean, basket?

Mr. MOSSINGHOFF. Well, it's the Bureau of Labor Statistics' constructs for these individual industries, where you take a representative basket of something, whether it's drugs or tires, or automotive parts, or whatever it is. That basket of drugs, in 1988, had an index based on 1967 of 350. For all other items, the normal inflation is at 370, and health care is at about 525. And there's no question that there has been inflation—that's one way to say it. And I can understand why the Committee would want to do that, but there are other ways to say it, too.

We're a declining share of the health-care dollar, and we save money. We're not the problem in the overall health-care problem. We're the answer.

The CHAIRMAN. Mr. Mossinghoff, I've asked what you would tell your constituents if you were a Senator and you lived in a State with a major elderly population. If you were standing behind the drug counter, and you were a druggist, and each month, almost, or every 2 or 3 months, when the same people that you know and sing in the choir with and have raised your children with, et cetera, come in and you say, oh, I'm so sorry, your drugs have gone up again—and they do, between 8 and 11 percent a year—if you were a druggist out there in Camden, AR, what would you tell those customers of yours?

Mr. MOSSINGHOFF. I think I'd attempt to tell them what I just said to you. But I'm not sure they'd be terribly persuaded, because that person has one thing on his mind. There already is a drug in existence thanks to us, that's why he's at the counter. There's a drug in existence and he'd like to get that drug for nothing if he could. He'd like you to pay him to take it, but he has to pay something for it, so it's a very difficult situation. I don't deny that at all.

But there is an overall socio-economic viewpoint that we think the Senate and the House had when they passed the Catastrophic Act, and that is to rely on marketplace forces.

The CHAIRMAN. We're not talking right now about the Catastrophic Act, Mr. Mossinghoff. We're talking about everyday USA out there, all across this country, and they've seen an 88 percent increase in drug prices and they're wondering why and they're wondering who is responsible.

Now they're really not only wondering, they're worrying, are they going to be able to afford these drugs to keep them alive. It's really that basic.

Now, remember, you're talking about the market basket of 350 drugs. These folks that come into your drugstore, Mr. Mossinghoff, they don't want to buy a basket of drugs. They don't know what a market basket is. They don't know what the GNP is. They don't know what's happened since 1968. They're worried about right now. And we can't explain nor can we justify these huge, enormous increases in prices, at the same time in profits, at the same time in tax subsidies by the American taxpayer, because all of these things that our Government is now giving to the manufacturers is not being passed on to the consumer, or to our Government.

Senator Warner.

Senator WARNER. Well, we certainly want to assure that person that he's getting the best quality to be found anywhere in the world, isn't that correct?

Mr. MOSSINGHOFF. It is correct. And the fact is that we're delighted that he could be at the counter, because that's the place——

Senator WARNER [continuing]. Or a lot of them wouldn't be there were it not for the advancements that your industry has made in the drugs?

Mr. Mossinghoff. That's exactly right. This committee, I guess, probably knows more than any single institution in the United States about the aging of America. But most of that aging, or a very high share of that aging, is because the magic medicines that are developed by our companies have succeeded in treating the acute illnesses that otherwise cause people not to age.

Senator Warner. But the Chairman has a legitimate question, and you have offered to help get us the answer.

Mr. Mossinghoff. Yes.

Senator Warner. Thank you.

The Chairman. By the way I've just been informed by the U.S. Capitol Police—to show this is an issue that has touched a nerve or a pocket book, or something—the U.S. Capitol Police said there were 500 people waiting in the Russell Building in another room waiting to get into this hearing. So, at any rate, there's a lot of interest in it.

Now, we mentioned a moment ago—in a moment I'm going to ask you about page 7 of your testimony—I have sent to you, or given to your associates, I think, Mr. Mossinghoff, this chart. And this chart indicates when a patent expires on a drug, say you've had it for 17 years and the patent expires on Brand X, we would normally think that the marketing forces, the free enterprise system that you've talked about, that we would see the price of Brand X drug go down when there was competition by the generics. This chart does not indicate that. This chart indicates that the price of Brand X, which is a brand drug, keeps going up. Why is this?

Mr. Mossinghoff. Mr. Chairman——

The Chairman. R&D is out, you've had your patent for 17 years, you've made a lot of dough on that particular drug, and the price still goes up. Why?

Mr. Mossinghoff. Well, we don't come anywhere near 17 years of protection on the patent.

The Chairman. Well, say 10 years.

Mr. Mossinghoff. I don't know what drug it is, and indeed as I responded to Senator Cohen, we cannot, PMA cannot, get involved in how our companies price. This says it's a typical drug, and I assume it's a drug. I assume you could find other drugs where the price goes down. But again, that's not something PMA would involve itself in. I assume it's one drug.

The Chairman. Well, this is done by the Aging Committee, our staff, so I know it's accurate or they wouldn't have done it. Maybe we can come back to that in just a moment.

Let's talk about taxes. Let's talk about page 7. And if you would like to review that page a moment. I'd like to ask you why, in your statement, you would have this committee believe that the basic taxes of the drug manufacturing industry have increased? Where do you substantiate that?

Mr. Mossinghoff. I'm sorry, Mr. Chairman, but are you saying the "costs of labor, material, taxes and promotion have also increased?"

[Subsequent to the hearing, the following information was received:]

Question. "I'd like to ask you why, in your Statement, you would have this Committee believe that the basic taxes of the drug manufacturing industry have increased? Where do you substantiate that?"

Answer. The U.S. Bureau of the Census collects financial data for manufacturing corporations and publishes these data for individual industries in the Quarterly Financial Reports (QFR). The data are published in the form of income statements and balance sheets. One of the data elements collected is "Provision for Current and Deferred Domestic Income Taxes."

The table below summarizes the tax data for the pharmaceutical industry published by the Census Bureau for 1981 through 1988. Because these data are collected through a statistical survey methodology, they are subject to some sampling variation. Thus, small differences in annual totals may not be meaningful. The data from 1981 through 1988, however, show an 86 percent increase in taxes for the industry.

Provision for Current and Deferred Domestic Income Taxes for the Pharmaceutical Industry

[In millions of dollars]

Year:	*Taxes*
1981	$1,196
1982	1,296
1983	1,680
1984	1,782
1985	1,655
1986	2,351
1987	2,280
1988	2,229

The CHAIRMAN. Yes.

Mr. MOSSINGHOFF. I'm trying to think where that came from. I did not do a lot of work on the taxes side in preparation for this statement. And if I misled the committee, I apologize for that.

The CHAIRMAN. I don't want to accuse you of misleading anyone. I've known you a long time and we've been personal friends, and we're going to be. We're not on the same side on this issue——

Mr. MOSSINGHOFF. If I may, let me respond to that question for the record.

The CHAIRMAN. Yes, sir.

Mr. MOSSINGHOFF. And with great apology if it turns out not to be the case.

The CHAIRMAN. Absolutely. I would like to have you take note of the Tax Analysts Organization of Arlington, VA: "Found that over the period of 1984 to 1987 the effective tax rate of the pharmaceutical manufacturers has declined 27 percent."

Now, in your advertising—and I'm not accusing you of misleading—I must say that your advertisements disappoint me. And I've seen all five of them. I clip your ads. And I bring them into the office. Now, listen, talk to us about this. For example, you talk about FDA. You're accusing FDA of the long pipeline. One reason for the long pipeline in FDA—because this is what we've got to be honest about—one reason FDA takes so long is that your organizations that you represent here today, the drug manufacturers are clogging the FDA pipeline with drugs that add nothing to existing therapies with C category drugs. We had a chart there just a moment ago, I wish you would put back up there now, David, showing how many C category drugs there are. You're clogging the—you've given the system high cholesterol. They can't do anything else except look at these C drugs, and they're not having an opportunity to look at those drugs that relate to Alzheimer's disease, to

AIDS, and all the rest, because you're clogging them with the profitable drugs. Is that right?

Mr. MOSSINGHOFF. That's not right, Mr. Chairman. For one, the statement that the C drugs don't do anything for anyone is just not supportable. The C drugs, as I've indicated, and we will provide information for the record, the C drugs are determined—going into FDA. And I don't see how you could say that the first Calcium Channel Blocker, which is state-of-the-art cardiovascular treatment now, or the first ACE Inhibitor, Zantac, which is the largest selling anti-ulcer drug in the world, haven't done anything for anyone. I really believe that statement is not supportable.

The CHAIRMAN. I'm going to need some of that ulcer medicine after this hearing. I should say that.

Now, let's talk about taxes just a moment.

Mr. MOSSINGHOFF. Second, the numbers—we will talk to your staff about these numbers. I suspect they're all NDAs—new drug applications. I don't know, maybe your staff could confirm that here.

The CHAIRMAN. I'm not sure. All I know is that the Food and Drug Administration is where we got the "me-too" factor.

Mr. MOSSINGHOFF. From 1981 to 1988, which is 7 years, there were not 300 new chemical entities filed——

The CHAIRMAN. That's 1981 to 1988——

Mr. MOSSINGHOFF. I don't know whether they are what's called new chemical entities, or whether they're new drug applications. Those are very different.

The CHAIRMAN. These are, I've been told, new drug applications.

Mr. MOSSINGHOFF. Not new chemical entities.

The CHAIRMAN. This is—or molecular entities——

Mr. MOSSINGHOFF. I think the numbers square with that. Now, what these are, Mr. Chairman, is if somebody has a dosage form, and they think there will be a more effective dosage form, or they can lower the dosage form, or they can change some other aspect of it, they still have to file a new drug application in order to do that. What that does is produce a greater variety for the physician to choose a new dosage form—and that needs a new drug application. These are not me-too drugs. These are simply changes in things which cannot be made without the approval of the Food and Drug Administration.

The CHAIRMAN. We may, Mr. Mossinghoff, come back to that point momentarily.

But my next point is about the inference you would have us draw from the pharmaceutical manufacturers that a drug costs $125 million to produce—the inference you would have us draw is that the companies are paying for all of this, that this is right out of your pocket, and you are good citizens, and I don't question that. Now, I want to ask you this question: Are you familiar with the research and development tax credit?

Mr. MOSSINGHOFF. Yes, sir.

The CHAIRMAN. Are you familiar with the area of the tax law called expensing R&D costs?

Mr. MOSSINGHOFF. Not really.

The CHAIRMAN. Well, your companies are, I promise you. What about R&D allocation?

Mr. Mossinghoff. Not enough to respond.

The Chairman. Your companies do. And what about the possession tax credit? I think that's Section 936.

Mr. Mossinghoff. I am familiar with that.

The Chairman. Puerto Rico.

Mr. Mossinghoff. I am familiar with that.

The Chairman. Right.

Now, those are four major areas. What are the States doing? Do they—don't respective States also grant some drug manufacturers the freedom from having their customers pay sales tax on items that they utilize and manufacture?

Mr. Mossinghoff. I don't know the answer to that.

The Chairman. And isn't certain income tax breaks also in R&D on the State level?

[Subsequent to the hearing, the following information was received for the record:]

Question. Don't respective states also grant some drug manufacturers the freedom from paying sales tax on items that they utilize and manufacture?

Answer. Most states exempt from sales tax the materials used in manufacturing a final product. The exemptions are the same for a pharmaceutical company as for any other manufacturer. We are unaware of any special exemption in any state that provides preferential tax treatment for drug companies over other manufacturers.

Many states do exempt drugs from a sales tax. The exemption reflects a state public policy that it is socially desirable to exempt certain basic items—drugs, clothes, food—from the state sales tax for the benefit of consumers.

Question. And aren't certain income tax breaks also in R&D on the state level?

Answer. Many states mirror the federal tax code, and therefore provide research and development credits, accelerated depreciation and other such measures for corporations. We specifically surveyed the tax laws of California, Indiana, North Carolina and New Jersey—states where there are substantial pharmaceutical operations—and found no preferential tax treatment for the pharamaceutical industry over other industries.

Mr. Mossinghoff. Again, I'm sure our tax committee can provide an answer. I don't know the answer.

The Chairman. You know where I'm headed. And that is that you're getting an awful lot of tax subsidies and tax breaks from the American taxpayer. So when you say it costs $125 million, really what you are doing, is you're doing what you're supposed to do. So I don't know why you brag about it. And I really don't think the drug manufacturers should brag about this. And I hope on your sixth ad, I think you've run five now—I keep up with them—on your sixth advertisement, I hope you might say also that we do get these tax breaks, folks, and hopefully if we can produce these drugs we can make a lot of them, and we'll pass the savings on to you. I wonder if your upcoming ad might do that.

Mr. Mossinghoff. If this is a question, let me attempt to respond. And that is to say, I heard your opening statement, and I have no basis at all for disagreeing with your estimate of a billion dollars a year in so-called tax breaks, of one kind or another. The $7.3 billion that our companies will invest this year is a significantly higher amount than that. And so I would submit that if it is a $1 billion figure, and I thought that's what I heard you say——

The Chairman. Yes, sir.

Mr. Mossinghoff [continuing]. That we're comparing $1 billion to $7.3 billion, $6.3 billion if you discount the $1 billion, and that would still put us way ahead of all other high-technology industries in the United States, where the average investment in R&D is 3.4 percent of sales.

The CHAIRMAN. Yes. Now, how much did you say you were going to invest, $7 billion?

Mr. MOSSINGHOFF. It's $7.3 billion this year.

The CHAIRMAN. All right.

Over the next 5 years, according to the Joint Committee on Taxation—I do not have this, and I hope I can document this momentarily—the Joint Committee on Taxation informs me that over the next 5 years there will be an $11 billion tax break for drug manufacturers. So you're going to come out ahead.

Mr. MOSSINGHOFF. Over the next 5 years?

The CHAIRMAN. Over the next 5 years, an $11 billion tax break for drug manufacturers for research and development.

Mr. MOSSINGHOFF. That's $7.3 this year. If you multiply that, and it's going up—it will double in 5 years. So it will be $14 billion in 5 years. If you integrate 7 to 14, I think you come out somewhere around $60 billion that we'll invest as compared with whatever number you have, the $11 billion. You can't compare a 5-year tax break to a 1-year expenditure. I think we're ahead of the game by about $50 billion that we're investing in new therapies.

The CHAIRMAN. All right, sir.

I don't want to push this point too much. I'm trying to maintain is that you get great inducement and incentive by our Government as a policy, and from the taxpayer of this country, in support of your research and development. I just hope you'll give us a break and tell people that that in fact is occurring.

Now, one final area in this concern. We give an R&D tax break for research for a new drug. And that's probably as it should be. Ultimately, FDA, let's say, approves the drug. That again is a U.S. Government function. The U.S. Government then grants a patent to that particular company to produce that drug for 17 years. For the costs of researching it, a tax break; a Government subsidy. Then, FDA approves the medicine, and then we move the plant to Puerto Rico to manufacture it. And get another tax break.

Now, how many of your members have plants that manufacture drugs in Puerto Rico, and take advantage of section 936 of the tax law?

Mr. MOSSINGHOFF. It's over 20, Mr. Chairman, over 20 of the largest——

The CHAIRMAN. It would be your major concerns.

Mr. MOSSINGHOFF. I don't think the smaller companies have it.

The CHAIRMAN. And do we know about how many employees that these companies have in Puerto Rico?

Mr. MOSSINGHOFF. It's well over 100,000. I'd have to confirm that for the record, because I didn't know this was going to be a hearing on Section 936.

The CHAIRMAN. Right. And the drugs manufactured there and the profits resulting therefrom, there's no tax liability, this is correct?

Mr. MOSSINGHOFF. I'm not sure it's no tax liability. It's reduced tax liability, I believe. Again, we can provide this information, and

I'm sure your staff can provide it. I don't believe it's no tax liability.

[Subsequent to the hearing, the following information was received for the record:]

Question. And do we know about how many employees that these companies have in Puerto Rico?

Answer. A 1987 study of Section 936 and Economic Development in Puerto Rico by Robert R. Nathan Associates, Inc. found that Section 936 companies employ 100,000 people and that an additional 175,000 people work for those who provide goods and services to Section 936 firms, for a total of 275,000 direct and indirect jobs. In addition, the Nathan study found that almost 62,000 jobs are directly and indirectly attributable to the pharmaceutical industry.

The jobs created by the pharmaceutical industry in Puerto Rico are primarily skilled jobs, for which the industry provides training and employee and family benefits. The pharmaceutical industry pays the highest average wages ($21,823 in 1983) among all Section 936 manufacturing industries.

The growth in Section 936 jobs has more than offset the significant decline in non-936 jobs in Puerto Rico, most of which are in labor-intensive industries. More than one-third of Puerto Rico's total employment is accounted for by the manufacturing operations of possessions corporations. Without Section 936, there would be much higher unemployment in Puerto Rico—and increased federal transfer payments.

Question. And the drugs manufactured there and the profits resulting therefrom, there's no tax liability? This is correct?

Answer. That is not correct.

Income earned in United States possessions, including Puerto Rico, Guam and the U.S. Virgin Islands, is subject to U.S. tax. Section 936 provides a credit, under specified conditions, offsetting the U.S. tax on income derived from the active conduct of a trade or business in U.S. possessions.

The intent of Congress in providing this tax incentive, as noted by the Senate Finance Committee as early as 1976, is to promote employment-producing investments by U.S. companies in Puerto Rico and other U.S. possessions. Under the Tax Reform Act of 1986, this objective was extended to include qualified Caribbean Basin countries. Congress has determined that the possessions tax credit is necessary to spur investment in areas of vital national interest where the cost of doing business would otherwise be prohibitively high.

Under carefully drawn regulations implementing the possessions credit, significant restrictions have been placed on the amount of active business or passive investment income that is eligible for the credit. In addition, Puerto Rico imposes a tollgate tax on possessions corporations earnings that are repatriated to parent companies on the U.S. mainland. Changes in Section 936 under the tax laws of 1982 and 1986 imposed additional restrictions on the amount of possessions-source income eligible for the credit.

The CHAIRMAN. Let's go back to our original chart; 88 percent increase in the cost of drugs, 28 percent in the inflation record. We've given all these tax breaks, you're going to Puerto Rico to manufacture the drugs. We've given you a patent, FDA approves, et cetera. What's the taxpayer getting out of all this?

Mr. MOSSINGHOFF. The taxpayer is getting an enormous saving in the rest of the health-care dollar because of the fact that we have, with all those intracorporate factors and forces, cut our share of the health-care dollar in half. The taxpayer is getting a better buy in 1988 on the basket full of drugs than he did in 1967.

The CHAIRMAN. I can't convince my constituents of that back home. Senator Cohen is much smarter than I am, and maybe he can.

Senator Cohen.

Senator COHEN. If I could come back to an issue raised by Senator Warner. He's attempted to highlight the ways in which market economies pertain to prescription drugs, that they're unique. But perhaps you could give us a little lesson here in terms of how this works. As I understand it, when we're talking about free market economy we have an arms length transaction, we have a skilled seller, and an informed or perhaps even gullible buyer, but a ready, willing and able buyer. That's how we normally define the free marketplace. But in this particular case we have someone other than the consumer who drives demand. And I would say the doctors and the hospitals in this particular case. You have somebody other than the consumer who's paying the bill. And that's Medicare, an insurance company, third party intermediaries.

And another point that strikes me as being somewhat ironic is that repeatedly you ask us to leave this to the free market system, and yet there appears to be some operations of monopoly power here, or monopoly pricing, whether the VA gets one price, or the Government gets another price, a hospital gets it for 1 cent, the pharmacy gets it for $32. I don't understand how you're talking about a free market economy in this situation where you don't seem to have that ready, willing, and able buyer, but in fact you have something other than the consumer driving this, or people other than the consumer making the decision. They're not informed.

Mr. MOSSINGHOFF. Senator, it's true that the marketing in the pharmaceutical industry is unique because there is a learned intermediary. As soon as drugs are safe and effective enough for self-medication, the companies, and typically our companies, will move them from prescription status to over-the-counter status. But during the time that a determination can't be made, or they're a potent medicine that needs to be monitored closely by a physician, it's the physician who makes the selection. And that's the way it works in this country. And it's a—I'd say again, very beneficial.

I think the evidence of the market economy is that in the Medicare Act itself, Congress set up the baseline period—1981 to 1986 is the standard of comparison—that the Prescription Drug Payment Review Commission looks at and the Secretary of HHS looks at. That period shows about a 10.2 percent increase in prices. In 1988, it's gone down to about 7.8. Now, that was the whole idea behind the 1984 Act—market economy. Then generics come onto market as soon as the patent expires, and that's not 17 years, I guarantee you. In fact, under the Act, it can't be more than 14 years. And at that point that was the cost-control measure adopted by Congress. It's significant, I think, that in those European countries which have a totally different system with regulated numbers of pharmacies, or even Government-owned pharmacies, those systems have not chosen to use generic incentives as a price control. They use direct market price controls, which is typical of some European countries. So I think there is a market working here. Clearly, in the case of the breakthrough drug, Tagamet, it's now got hefty competitors in Zantac, Axid, and Pepcid. Now, that is a market economy well at work.

I think the industry itself is sort of a free-enterprise, liberal economist's dream. It's highly competitive with nobody controlling more than 8 percent of the market. Twenty-two companies would have to be put together to reach 75 percent of the market. The industry has a positive trade balance. It does all of its R&D, albeit we think with some appropriate incentives from the taxing side. It produces the most cost-effective form of therapy, and it is a declining share of the health-care dollar. I think the market's the place. I think the fact that in 1988, if you can say to your constituents that drugs, the basket full of drugs cost less now than it did in 1967, if that's not free-market forces at work, I don't know how you would define free-market forces.

Senator Cohen. But I do know that PMA is usually in lobbying for more protection rather than less, as far as patents are concerned. You didn't ask for a lower period of time, but a greater period of time.

Mr. Mossinghoff. That's exactly right. I mean, we work around the world for intellectual property protection.

Senator Cohen. Is that free market, or is that monopolistic?

Mr. Mossinghoff. I have a bias because I'm a former patent commissioner during 1981 and 1985. But I think patents are the absolute essence of free market. You spend your own money. You take nothing away from the market that was there. What you do is add something to the market, and in return for your enormous expenditure, the $125 million, you get a patent on the thing you brought to the market. It takes nothing away from the market. On the new thing you brought to the market, you use the patent as your incentive to do free-enterprise investment. It's the essence of the free-market system.

Senator Cohen. Did you want to stick with that $125 million figure?

Mr. Mossinghoff. Very definitely.

Senator Cohen. So, without responding to the question about the tax credits, the expensing of R&D——

Mr. Mossinghoff. Well, I think that is based on our R&D expenditures. It was a study done by Professor Wiggins of Texas A&M. Another study was done, an earlier study by Professor Hansen. There's yet a third study by Professor Grabowski at Duke University who said it's $132 million. While we can't prove that it's $125 million versus $132 million, all the studies fall in exactly that range. Now we could, I think, calculate. An economist could find out what the tax situation was and find out how much of that $125 million is the R&D tax credit.

Senator Cohen. I just have a conceptual problem in dealing with a situation in which demand is being driven by those who pay very little for a drug. Where you create a demand by giving it away to a hospital, or giving it away to an attending physician, and then when it gets out into the marketplace the price goes up 30 times. Now, that to me—we see that illegally taking place on the streets of Washington, DC, and we see it as a criminal act. That's how they get people hooked, low price and then jack the price up once people become addicted to that particular drug. And it just seems to me—I'm not suggesting this, but in this particular case, demand is being driven by people who don't bear the cost. They're not the ones. They're being passed on down the line to people who have no idea what's involved. And I don't think that necessarily is a free market economy that we're talking about.

Mr. Mossinghoff. I'm not sure they have no idea what's involved.

Senator COHEN. They have an idea when they have to pay the bill, but they don't understand why.

Mr. MOSSINGHOFF. But I think that——

Senator COHEN. We don't even understand why.

Mr. MOSSINGHOFF. One of the advantages of a policymaker—and I would sympathize with the person standing at the counter in Arkansas, because that person is not charged with policy—is you stand back and look at that system. Drugs cost less now than they did in 1967, and they produce marvelous recovery. You know, the aging of America is really due in large part to what has been referred to as enchanted substances, that our companies make. They're not the problem. They're a declining share of the healthcare dollar, and they're the most cost-effective share. So I think as policymakers, you'd stand back and look at the whole health care system.

Senator COHEN. The ball's back to you, Mr. Chairman.

The CHAIRMAN. Many of the companies that comprise your association, Mr. Mossinghoff, have submitted, I believe, five or six letters this morning, back to Kansas where they said they would not negotiate, nor do business with these buying groups that are attempting to get a better price for the consumer back in the State of Kansas. Have any of these companies, to the best of your knowledge, consulted an attorney to ask if this refusal is a violation of the Robinson-Patman Act?

Mr. MOSSINGHOFF. I don't know the answer to that.

The CHAIRMAN. I don't know either. But I think it's a question that ought to be asked.

Mr. MOSSINGHOFF. In a general comment, that act was a Depression Era act, together with the nonprofit institution exception or exemption to it. That's been litigated, I believe, four or five times. And I mentioned the major cases in a footnote to my statement. The last one, I believe, was in 1984. So apparently the act itself, since it gives private parties, aggrieved parties, a private cause of action, and since unfortunately in the United States no one is terribly reluctant to sue their neighbor, I would submit that the act and its exemption are probably pretty well understood by the industry. Those were four cases directly involved in the pharmaceutical industry.

The CHAIRMAN. Mr. Mossinghoff, I would just conclude with a paragraph or so. I don't know what the outcome of this hearing will be. I know we're going to have another one. And I certainly don't know what the Senate or the House will do. I have no idea. I don't know in what year we'll do it. But I can say one thing. This system, this legislative system that we have, and you know it very well, as well as anyone in this town, we very seldom act, we react. And if that red line keeps going up at that rate, and Senator Pryor, and Senator Cohen, and all of us can't go back there and explain this to our constituents, and if that druggist cannot explain this to his or her customers, I don't know when it will happen, but something is going to happen. Something's going to give.

I want to thank you for your testimony.

Mr. MOSSINGHOFF. And thank you for permitting me to be here.

The CHAIRMAN. Thank you very much.

We'll call our next panel now. That's Mr. Joseph Thomas III, Ph.D., of Purdue University School of Pharmacy, and Mr. Bruce Laughrey, President of Medi-Span Inc., Indianapolis, IN. Gentlemen, we appreciate your patience. You've been long suffering sitting here in this meeting. It's been a warm and crowded room all day. And we look forward to your statement. We will try to consist of no more than five minutes each. We'd appreciate your staying within that time frame, and then I'll have a few questions.

Dr. Thomas, you may begin.

STATEMENT OF JOSEPH THOMAS III, PH.D., OF PURDUE UNIVERSITY SCHOOL OF PHARMACY, WEST LAFAYETTE, IN

Mr. Thomas. Thank you for the opportunity to provide comments this afternoon.

Although drug expenditures represent less than 7 percent of total health care expenditures, the expenditures made on prescription drugs have come under increasing scrutiny since drug price increases began outpacing general price increases during the 1980s. However, community pharmacies have not benefited from increases in prescription drug prices. Instead, increases in prescription drug prices and heavy competition have decreased pharmacy owners' financial returns.

Some pharmacies' very survival is in doubt as they are caught between the squeeze of increasing product costs, intense competition, and restricted third party reimbursement rates. If you look at the table to your far left, Senator, you can clearly see that increased pharmacy profits have not been the driving force behind prescription price increases. The average price of a prescription dispensed in retail pharmacies increased from $3.35 in 1965 to $4.64 in 1975. Between 1975 and 1987, the average retail prescription price tripled to over $15. However, independent pharmacies' net profit before taxes on sales declined from 5.8 percent in 1965 to only 3.3 percent in 1987.

The data clearly show that independent pharmacies have experienced decreased profitability during this era of rapidly increasing prescription prices.

Product costs, the amount that pharmacists spend to purchase drug products from manufacturers and wholesalers, represent the largest expense category in community pharmacies. In fact, product costs increased from 63.8 percent of independent pharmacy sales in 1965 to 67.4 percent in 1985. As a result, pharmacy gross margins have declined from more than 36 percent of sales in 1970 to less than 33 percent in 1985. Gross margin represents the fraction of sales revenue left to pay operating costs, such as rent, heat, air conditioning, or employee wages, after product costs have been subtracted.

A decline of 3 to 4 percent over a 10-year period might at first glance appear insubstantial. However, it is instructive to note that in 1987, independent pharmacies 'average net profit before taxes was only 3.3 percent based on Lilly Digest data. It is clear that pharmacies have not benefited from drug product price increases. Instead, prescription drug costs have become a financial burden to retail pharmacies.

Reimbursement rates under Medicaid have been a contributing factor in this cost-price squeeze. Medicaid covered 17.7 percent of all retail prescriptions in 1987. However, prescriptions covered under Medicaid represented 21.4 percent of all prescriptions dispensed by independent pharmacies, as compared to only 10.4 percent of prescriptions dispensed by chain drug stores in 1987. The $14.39 average Medicaid prescription reimbursement in 1987 represented a 13-percent increase over 1986. But more informative is the fact that the $11.07 average product cost in 1987 represented a 19.6-percent increase from 1986. In contrast, the $3.32 average pharmacist dispensing fee represented a 4.6-percent decrease from 1986.

The percentage of the average Medicaid prescription that remained after accounting for drug product costs to cover pharmacies' operating expenses, or to contribute toward some return on a pharmacy owner's investment, has decreased from 33.2 percent in 1982 to 23.1 percent in 1987 under Medicaid. As stated earlier, over 70 percent of Medicaid revenue in community pharmacies goes to pay for drug product costs that pharmacists incur in purchasing products from drug wholesalers or manufacturers.

Pharmacies have little control over product costs. Since pharmacies have little control over their product costs, incremental restrictions on reimbursement for retail pharmacists have not been and will not be effective in controlling or reducing prescription drug program benefits. Efforts to contain costs such as initiatives to discount AWP in estimating product acquisition costs under Medicaid ignore the fact that total pharmacy reimbursement consists of the product cost component and the pharmacy dispensing fee.

If additional restrictions are placed on pharmacy reimbursement, some pharmacies will be forced out of business. In fact, pharmacies that tend to be located in areas with higher concentrations of Government program beneficiaries, such as independent pharmacies, are likely to feel the greatest impact of such restrictions.

In summary, since pharmacies have little control over drug product costs, restrictions on retail pharmacy reimbursement cannot be effective in containing program costs. However, such restrictions present a very real threat to the survival of many pharmacies, and to program beneficiaries' access to pharmaceutical services.

[The prepared statement of Mr. Thomas follows:]

TESTIMONY OF

JOSEPH THOMAS III, Ph.D.
ASSOCIATE DIRECTOR
PHARMACEUTICAL ECONOMICS RESEARCH CENTER
SCHOOL OF PHARMACY, PURDUE UNIVERSITY

Mr. Chairman, my name is Joseph Thomas III. I serve as associate director of the Pharmaceutical Economics Research Center, in the Purdue University School of Pharmacy.

Introduction

Health expenditures have exhibited a long-term growth trend in terms of total dollars expended on health care and the percentage of the nation's gross national Product (GNP) that has been consumed by health care expenditures. In 1970 annual health care expenditures totaled $75 billion and 7.4 percent of GNP. In 1987 total health expenditures were $500 billion and 11.1 percent of GNP (Figure 1).

Total expenditures on drugs and medical sundries have also shown continuing increases since 1950. In 1950, such expenditures were $1.7 billion. In 1970 drugs and medical sundry expenditures equalled $8.0 billion. By 1987 drug and medical sundry expenditures had risen to $32.8 billion. However, Expenditures on Drugs have accounted for a declining percentage of total health care expenditures over the past three decades. Drugs accounted for 13.6 percent of total health care expenditures in 1950, 10.7 percent in 1970, and only 6.8 percent in 1987 (Figure 2).

Although drug expenditures represent less than 7 percent of total health care expenditures, the expenditures made on prescription drugs have come under increasing scrutiny. Part of the reason behind the increased attention is the fact that prescription drug price increases began outpacing general price increases during the 1980's. Prior to the 1980's, prescription drug prices increased at a slower rate than increases in the consumer price index (CPI). However, during the 80's increases in the CPI for prescription drugs have outpaced general inflation as represented by the CPI for all items (Figure 3).

Pharmacies have not Benefited from Prescription Price Increases

As a result of the rapid increases in prescription drug prices, pricing practices of all sectors involved with pharmaceuticals, including community pharmacies, have come under review. However, community pharmacies have not benefited from increases in prescription drug prices. Instead increases in prescription drug prices and heavy competition have decreased pharmacy owners' financial returns. Some pharmacies' very survival is in doubt as they are caught between the squeeze of increasing product costs, intense competition and restricted third party reimbursement rates.

The average price of a prescription dispensed in retail pharmacies increased from $3.35 in 1965 to $4.64 in 1975. Between 1975 and 1988 the average retail prescription price almost tripled to over fifteen dollars. However, independent pharmacies' net profit before taxes on sales declined from 5.80 percent in 1965 to only 3.20 percent in 1988 (Figure 4). . Clearly increased pharmacy profits have not been the driving force behind prescription price increases. Instead, the data clearly show that independent pharmacies have experienced decreased profitability during an era of rapidly increasing prescription prices.

Pharmacies Are in a Cost-Price Squeeze

Product costs, the amount pharmacists spend to purchase drug product from manufacturers and wholesalers, represents the largest expense category in community pharmacies. In fact, product costs increased from 63.8 percent of independent pharmacy sales in 1965 to 67.4 percent in 1985 (Figure 5). As a result, pharmacy gross margins, have declined from more than 36 percent of sales in 1970 to less than 32 percent in 1988 (Figure 6). Gross margin represents the fraction of sales revenue left to pay operating costs such as rent, heat, air conditioning, telephone bills, or employees wages after product costs have be subtracted A decline of between 3 and 4 percent over a ten year period in pharmacy gross margins might a first glance appear insubstantial. However, it is instructive to note that independent pharmacies' average net profit before taxes was only 3.20 percent as reported in the *Lilly Digest*.

Pharmacists have responded in part to increasing product costs and declining gross margins by attempting to reduce operating expenses. In fact, operating expenses as a percentage of sales declined from 23.3 percent in 1973 to 28.8 percent in 1987. Even though pharmacies have managed to reduce their operating expenses as product costs have increased they have not been able to maintain their profit margins. Independent pharmacies' net profit before taxes declined from 5.8 percent of sales in 1965 to 3.2 percent of sales in 1988 (Figure 4).

In other words, pharmacies have been squeezed because product cost have been increasing when pharmacies have been restrained from increasing revenue. Due to the cost-price squeeze pharmacies have been forced to absorb some of the product cost increases in the form of reduced net profit. It is clear that pharmacies have not benefited from drug product price increases. Instead, increased prescription drug costs have become a financial burden to retail pharmacies.

Impact of Government Programs

Medicaid covered 17.7 percent of all retail prescriptions in 1987. However, prescriptions covered under Medicaid represented 21.4 percent of all prescriptions dispensed by independent pharmacies as compared to only 10.4 percent of prescriptions dispensed by chain drug stores in 1987. The average prescription reimbursement under medicaid in 1982 was $9.17 of which $6.13 went to cover product costs and $3.04 represented pharmacists' fees. By 1987 the average prescription reimbursement under medicaid was $14.39 of which $11.07 went to cover product cost but only $3.32 was for pharmacist fees (Figure 7).

The $14.39 average Medicaid prescription reimbursement in 1987 represented a 13 percent increase over 1986's $12.74. But more informative is the fact that the $11.07 average product cost in 1987 represented a 19.6 percent increase from $9.26 in 1986. In contrast, the $3.32 average pharmacist fee represented a 4.6 percent decrease from 1986.

More or less static pharmacy fees under medicaid while pharmacies have been incurring increased product costs have resulted in declining gross margin on Medicaid prescriptions for community pharmacies. For example, in 1982 drug product costs represented 66.8 percent of the average Medicaid prescription reimbursement to pharmacies. In 1987 the proportion of the average Medicaid prescription reimbursement that went to pay prescription drug product costs had increased to 76.9 percent. In other words, the percentage of the average Medicaid prescription reimbursement that remained, after accounting for drug product costs, to cover pharmacies operating expenses or to contribute toward some return on a pharmacy owner's investment had decreased from 33.2 percent in 1982 to 23.1 percent in 1987 (Figure 8).

Limiting Pharmacies' Reimbursement Will Not Control Benefit Program Expenditures

As stated earlier, over 70 percent of each dollar of revenue in community pharmacies goes to pay for drug product costs that pharmacies incur in purchasing drug products from drug wholesalers or manufacturers. Pharmacies have very little control over drug product costs. The cost to retail pharmacies for a given product may change several times during the course of a year without prior notice.

Since pharmacies have little control over their drug product costs, incremental restrictions on reimbursements for retail pharmacies have not been and will not be effective in controlling or reducing expenditures on prescription drug benefit programs. Efforts to contain costs, such as initiatives to discount AWP in estimating product acquisition cost under Medicaid ignore the fact that total pharmacy reimbursement consists of both the product cost component and the pharmacy dispensing fee. Pharmacies' dispensing fees under Medicaid have experienced negligible increases over the past decade. In fact, Medicaid dispensing fees have actually decreased in real dollar terms over the past decade (Figure 9). Even with additional restrictions on retail pharmacy reimbursement, program cost will continue to increase as pharmacies experience increased product cost over which they have little control. However, such restriction will exacerbate the cost-price squeeze faced by retail pharmacies.

Some might suggest that any deficiencies in reimbursement under government programs can be made up through minor increases in charges to cash paying customers. However, as the proportion of retail pharmacy prescriptions covered under government programs increases, necessary additional charges to cash paying customers to make up for deficiencies in government reimbursement increases exponentially, not in proportion to increases in prescriptions covered under government programs.

More importantly, competition in the retail pharmacy market will not permit pharmacies to pass such increases on to private third party programs or cash paying customers. Since differences exist across pharmacies in the proportion of their prescriptions covered by government programs, the necessary increase in charges would vary across pharmacies. For example, on average the proportion of prescriptions covered by Medicaid in independent pharmacies is twice as large as in chain pharmacies. Therefore Independent pharmacies would have to charge much higher prices on all other prescriptions in order to maintain financial viability. However, each pharmacy is caught in a dilemma because consumers will choose to have their prescriptions filled at pharmacies that offer lower prices. In reality, in the competitive retail pharmacy market, pharmacies can not make up deficiencies in reimbursement under government programs through higher charges to other customers.

If additional restrictions are placed on pharmacy reimbursements some pharmacies will be forced out of business. In fact, pharmacies that tend to be located in areas with higher concentrations of government program beneficiaries, such as independent pharmacies, are likely to feel the greatest impact of such restrictions. Therefore, such restrictions are likely to cause closures of some pharmacies, especially independent pharmacies that typify small business enterprise. Since the pharmacies most likely to close are those serving large number of government program beneficiaries such closures will also significantly reduce access to pharmaceutical services for such program beneficiaries.

In summary, since pharmacies have little control over drug product costs, restrictions on retail pharmacy reimbursement can not be effective in containing program costs. However, such restrictions present a very real threat to the survival of many pharmacies and to program beneficiaries' access to pharmaceutical services.

Figure 1:

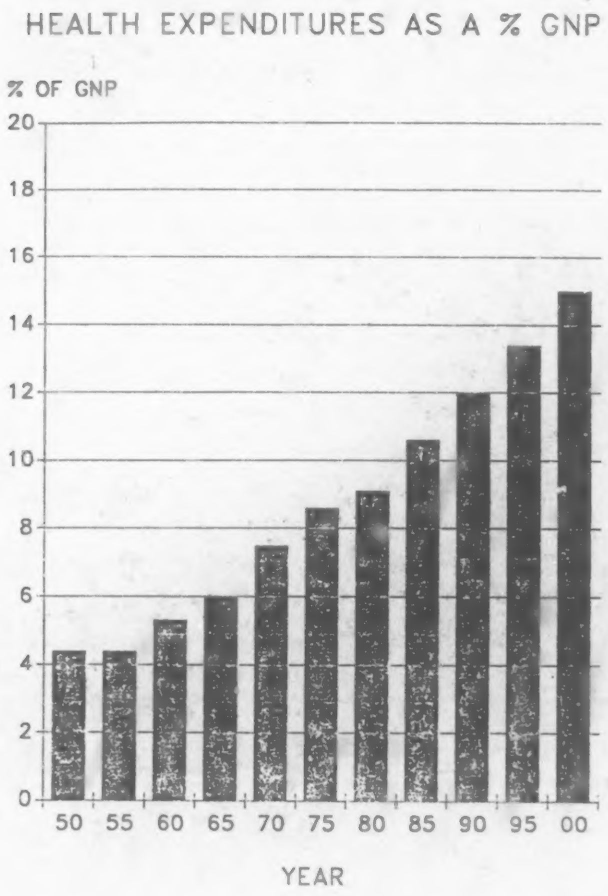

HEALTH EXPENDITURES AS A % GNP

Figure 2:

DRUGS AS A % OF NATIONAL HEALTH EXPENDITURES

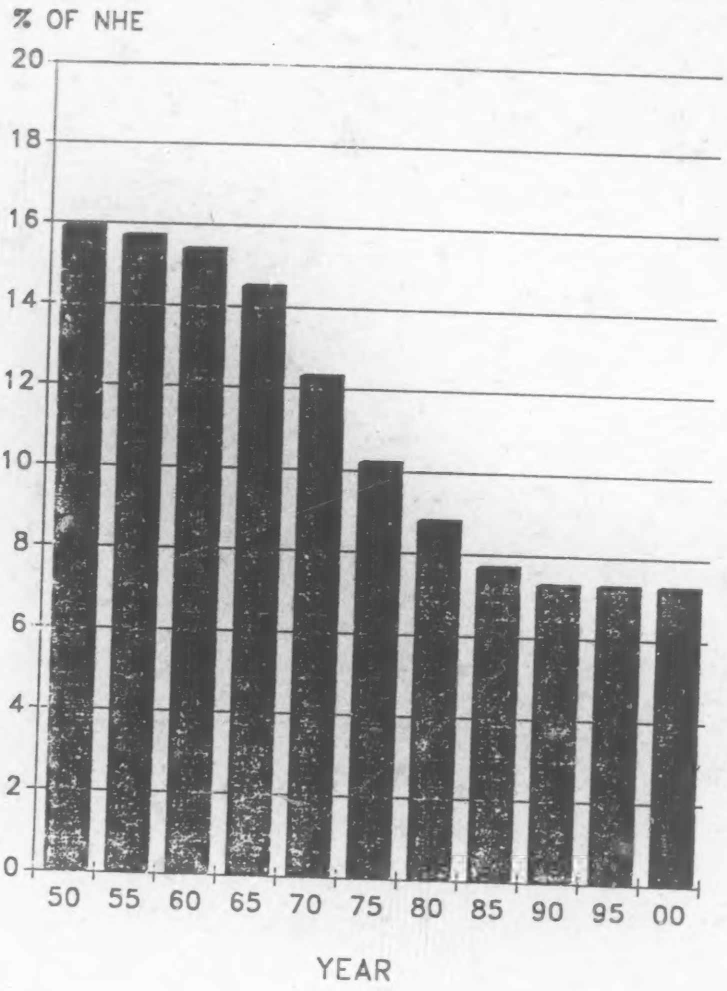


Figure 3:

CPI FOR ALL ITEMS AND RX DRUGS: ANNUAL PERCENT CHANGE

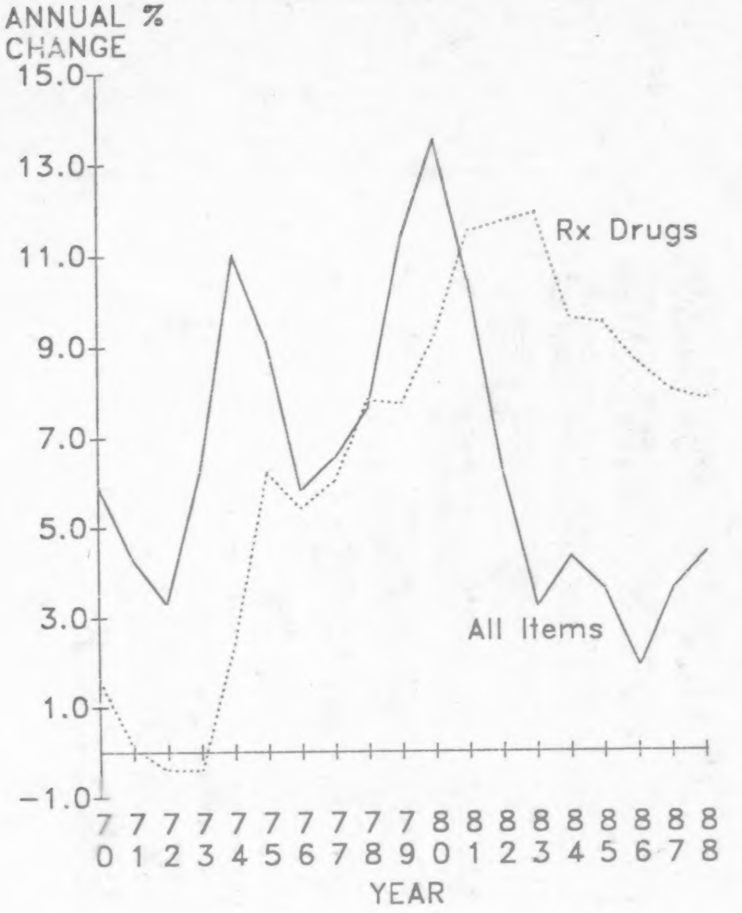


Figure 4:

AVERAGE RX PRICE AND PHARMACY NET PROFIT:
1960–1988

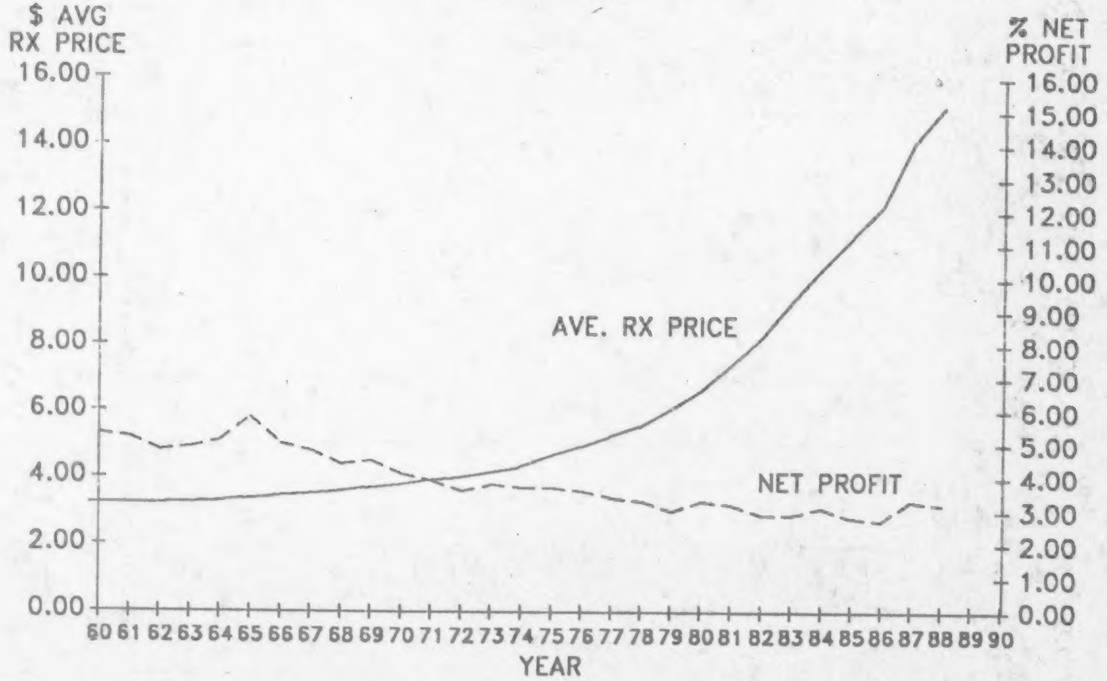
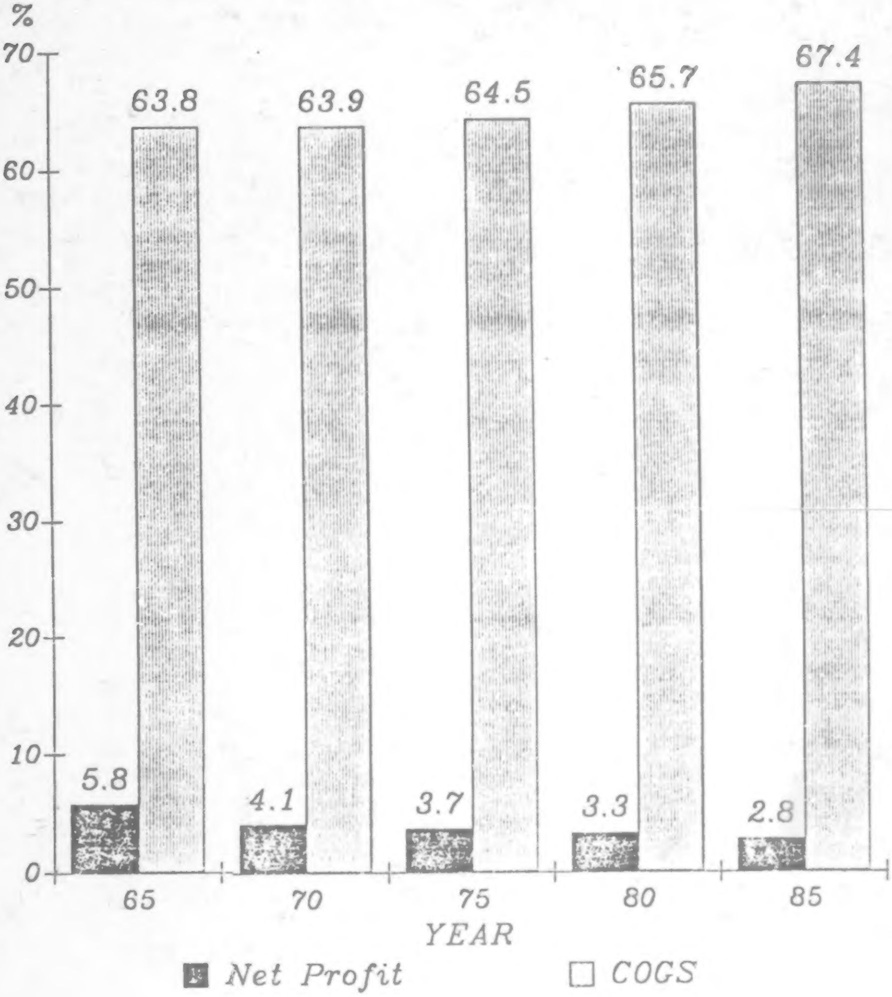


Figure 5:

Product Costs and Net Profit in Each Pharmacy Sales Dollar



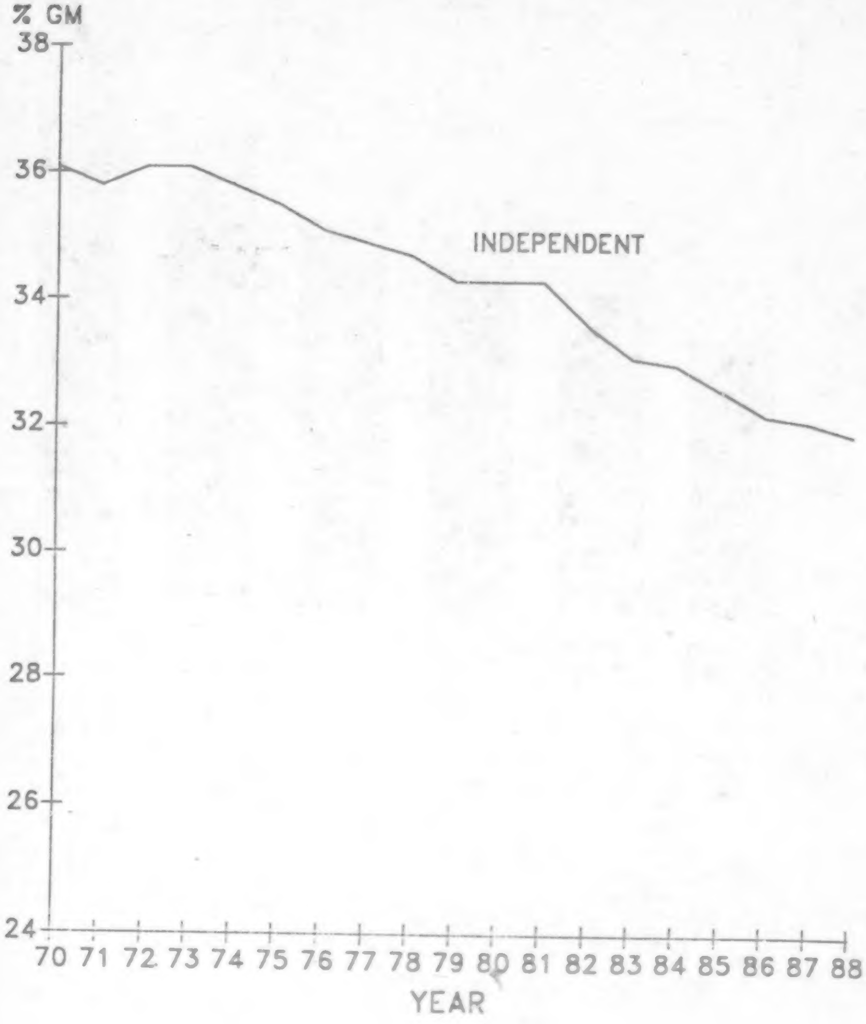


Figure 6:

% GROSS MARGINS IN RETAIL PHARMACY

Figure 7:

MEDICAID RX PRICE COMPONENTS

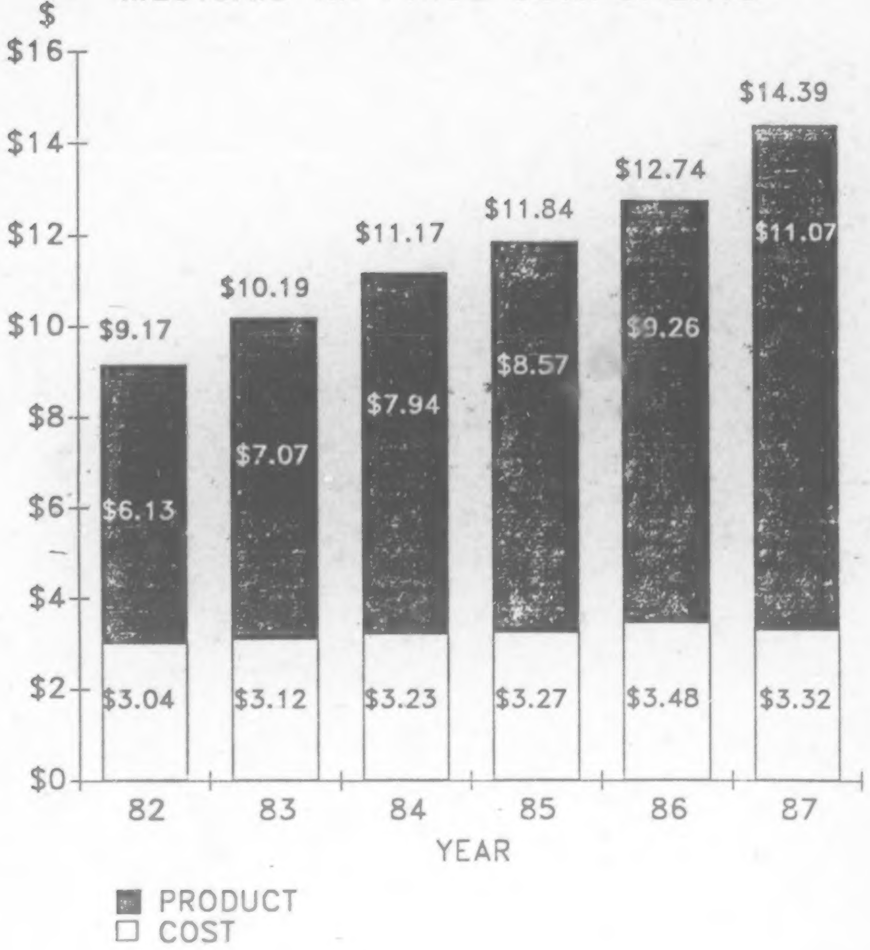


Figure 8:

DRUG PRODUCT COST AS A % OF TOTAL MEDICAID RX PRICE

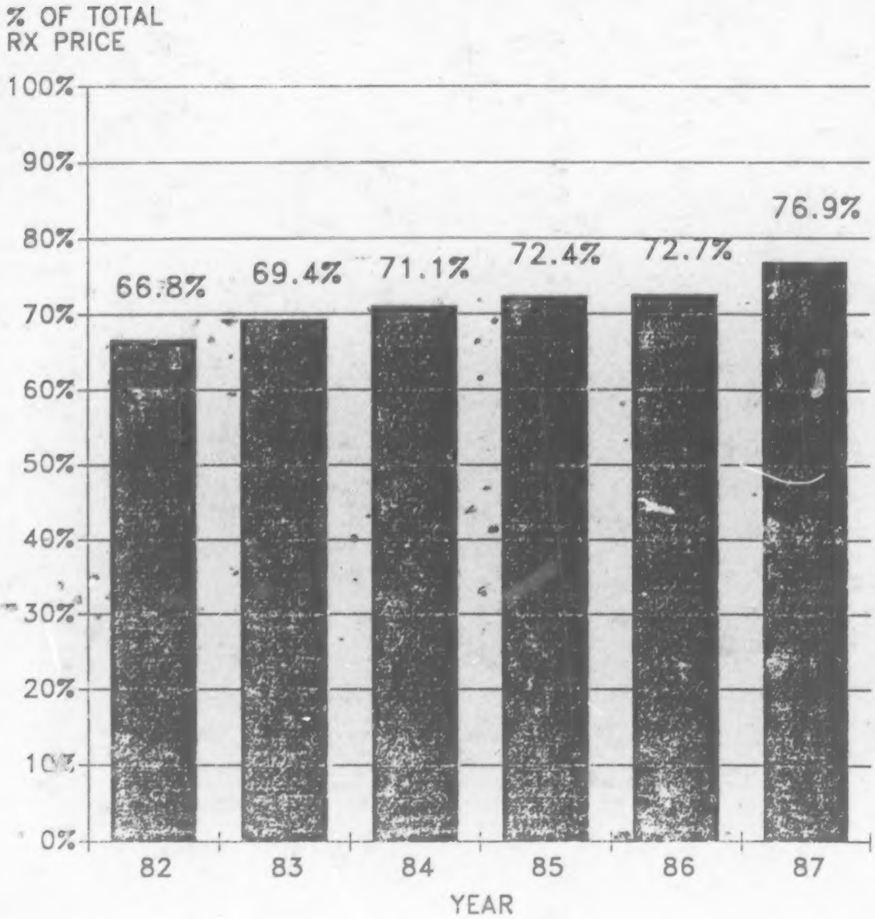
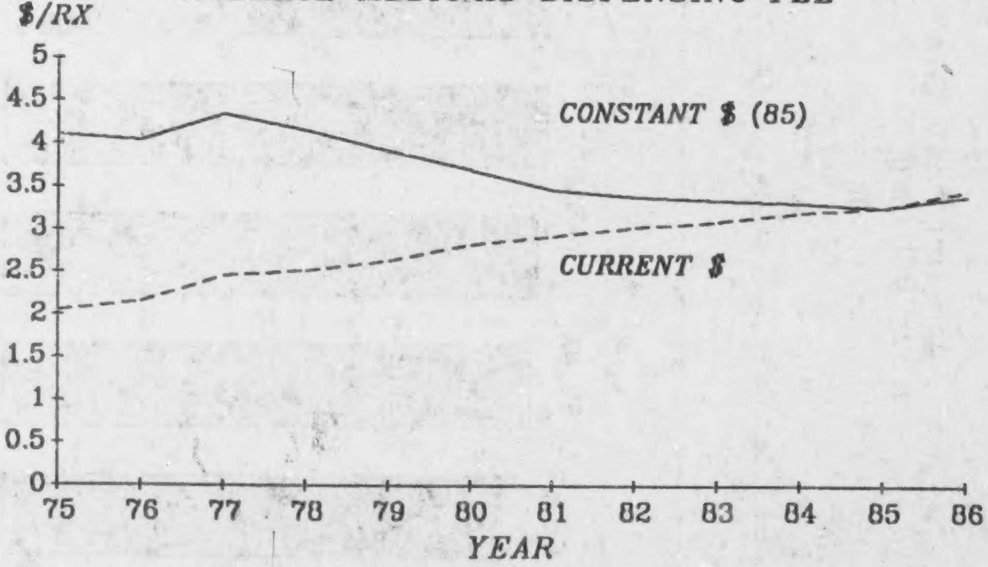


Figure 9.

AVERAGE MEDICAID DISPENSING FEE



Response to question: Are Medicare reimbursement rates for prescriptions generous to pharmacies.

(To be inserted following prepared comments)

The Medicare Catastrophic Coverage Act of 1988 established a program of coverage for outpatient prescription drugs for persons electing Part B coverage under Medicare. The Act provides for reimbursement to participating pharmacies for prescriptions for single source drugs based on the lower of: (1) the average wholesaler price (AWP) for the drug dispensed plus $4.50 as a dispensing fee, (2) the pharmacy's usual and customary charges, or (3) the 90th percentile of usual and customary charges for like prescriptions in other pharmacies.

Reimbursements to pharmacies for prescriptions for multisource drugs are based on the lower of: (1) the pharmacy's usual and customary charges or (2) the median AWP for the drug entity dispensed plus $4.50 as a dispensing fee. Cursory comparison of the reimbursement formula under medicare with other programs have lead some to mistakenly assume that Medicare reimbursement for participating pharmacies is generous. However, careful consideration of the Medicare reimbursement formula and the unique aspects of the Medicare formula in contrast with other programs reveal that Medicare reimbursement to participating pharmacies is fiscally conservative.

Because of the "lower of clause" in the Medicare reimbursement formula, under no circumstances will a pharmacy be reimbursed more under Medicare for filling a prescription than the pharmacy would normally charge non-Medicare purchasers. If, for any reason, a pharmacy's usual and customary charge for a prescription is less than the sum of the average wholesale cost of the ingredient and the $4.50 dispensing fee, the pharmacy will be reimbursed the lower amount. Reimbursement for prescriptions for single source drugs is also limited not only to the individual pharmacy's usual and customary charge but to the 90 percentile of usual and customary charges for like prescriptions in all pharmacies.

The average wholesale price (AWP) for products dispensed in pharmacies will be set and updated only semi-annually. Yet, pharmacies experience product price changes throughout the year. Therefore, pharmacies will have to accept fixed reimbursement levels for a six month period although product costs may have increased during the period.

Moreover, the AWPs on which pharmacies will be reimbursed for their product costs will be 6 months out-of-date at the beginning of the period in which they are set. For example, AWPs on which pharmacies' reimbursement levels will be based for the period from January 1 to June 30 of each year will be based on prices being paid by pharmacies on July 1 of the previous year. Since the AWPs are 6 months out-of-date at the beginning of the period and are held fixed for 6 months, the AWPs will be 12 months out of date before they are updated. The net effect of using out-of-date AWPs and the lag in updating AWPs is that pharmacies will receive product reimbursement that is less i.e., effectively discounted, from what pharmacies would receive if they were actually reimbursed at updated AWP levels.

The 90th percentile limit for reimbursement on prescriptions for single source drugs will also be based on usual and customary charges 12 to 18 months out-of-date. Thus, the maximum reimbursements to pharmacies on single source prescriptions will be capped at levels that do not reflect inflation during the previous 12 to 18 months. The use of dated AWPs, the use of dated usual and customary ceilings for reimbursements on prescriptions for single source drugs, and lags in updating the AWPs on which pharmacies' reimbursement is calculated will result in Medicare reimbursement levels for pharmacies will be substantially less than AWP plus the $4.50 dispensing fee.

Even if Medicare did not use dated AWPs and lag updating of AWPs, the "lower of" clause would ensure that pharmacies receive no more than their usual and customary charges for any prescriptions dispensed. However, the use of dated AWPs and lags in updating AWPs combined with "lower of" clauses will result in reimbursement levels for pharmacies that are not generous. In fact, concern might more appropriately be placed on whether the current reimbursement basis and schedule for updating reimbursement rates are ones which will allow pharmacies to actively participate in the Medicare program.

The CHAIRMAN. Dr. Thomas, thank you. I'll have a couple of questions in a moment.

Mr. Laughrey.

STATEMENT OF BRUCE LAUGHREY, R.PH., PRESIDENT OF MEDI-SPAN, INC., INDIANAPOLIS, IN

Mr. LAUGHREY. Mr. Chairman, my name is Bruce Laughrey. I'm the President of Medi-Span, Inc. of Indianapolis, IN.

Medi-Span is a privately held corporation whose primary business is the collection of data and publishing of information concerning pharmaceuticals for the health care industry. Our customers include retail pharmacists, drug chains, manufacturers, wholesalers, insurers, third party administrators, health management organizations, hospitals, and physicians. And we're pleased to accept this invitation to testify before this committee, and to share information concerning pharmaceutical pricing trends.

Now, Medi-Span's prescription pricing guide was first published in 1977 as a monthly publication listing average wholesale price and manufacturer direct price for approximately 6,000 of the most commonly used prescription drug pharmaceuticals. As a reference in my documentation, Figure 1 represents one of the pages from that document.

Now, over the past 12 years Medi-Span has introduced a variety of printed publications, as well as expanded into providing computerized data bases of pharmaceutical information, and electronic media to support numerous computerized applications. Today Medi-Span's master drug data base, a core file of information, contains current as well as historic price information on over 100,000 pharmaceutical and health-related products in the U.S. market.

The published average wholesale price, or AWP, is a key index price included in both our printed and electronic publications. This AWP is widely accepted and used in the industry as a basis for the purchase of drug products. In addition, many third party payers of prescription insurance benefits reimburse pharmacists on the basis of a professional fee plus the cost of medication provided. The published AWP is used as the cost component in the reimbursement format. The published AWP is obtained directly from over 600 pharmaceutical manufacturers, distributors, and wholesalers. We validate this information published by using multiple information sources where feasible.

We would like to clarify that the published AWP is a standard reference price and does not recognize earned discounts for quantity purchases, bidder contract pricing, or other forms of trade discounts; thus, the AWP price is the price that the pharmacy would typically pay if they purchased a single bottle of the item from a local drug wholesaler. The published AWP remains the only consistent price index that is useful for comparative purposes.

Much of the comparative average wholesale price information we were requested to provide is included in one of our publications, the Generic Buying and Reimbursement Guide, which is shown in figure 2. The GBRG, as we call it, is a quarterly publication subscribed to by thousands of pharmacies as an aid in selecting the most economical, therapeutic equivalent product available in the marketplace. By including the average wholesale price information along with the FDA therapeutic equivalence evaluation code, the Orange Book rating, product selection, and buying decisions are greatly enhanced.

The invitation to testify asked us to examine the pricing patterns of a specific set of drugs by referring to the AWP histories maintained in our master drug data base. This set of 10 single source items frequently used by the elderly were found to have increased AWP at an annual average rate of 9.2 percent between January 1, 1982, and December 31, 1986. I refer you to table 1. This same set of single source drugs averaged a 7.9-percent AWP increase in 1987, and a 9 percent AWP increase during 1988.

A set of 35 multiple source drugs frequently used by the elderly was also examined to determine AWP changes between 1982 and 1988. The originator brands of these multiple source drugs had an average annual AWP increase of 9.9 percent between 1982 and 1986, as referenced in table 2. In 1987 the average annual AWP increase was 6.9 percent, and in 1988, AWP increased by 6.4 percent, for the originator brands of this group of multiple source products. Not all of the multiple source drugs were off patent during the entire period of 1982 to 1986. More than one-third of the drugs in this group were still under patent protection for at least a part of the period of 1982 to 1986.

It is noteworthy that the originator brands in both the single source drug group and the multiple source drug group had similar annual rates of increase in AWP between 1982 and 1986, with increases of 9.2 percent and 9.9 percent respectively. And I reference figure 3.

It appears that, in general, single source drugs in a period just prior to patent expiration do not experience a slowed or declined rate of AWP increases, but rather the AWP changes continue for these products at rates similar to single source products. Now, once drug products have been off patent for several years, their rate of AWP increase does appear to moderate somewhat with respect to the rate of increase in AWP for single source products. The originator brands of multiple source drugs had lower annual AWP increases than single source drugs in both 1987 and 1988. The originator brand products tend to continue AWP price increases at about the same or slightly lower rates as when the product was patent protected. This trend persists despite the fact that generic products may be introduced into the market, and may experience significant competition and decreases in AWP price.

The price change patterns of all brand name manufacturers should not be painted with a single broad brush. In examining changes in AWP over time as products go off patent, one notes patterns unique to specific drug companies and to specific drug categories. During 1987, for example, 11 of the 35 originator brands of multiple source drugs had no increase in AWP, while another 7 of the 35 had increases of 10 percent or more.

The CHAIRMAN. Mr. Laughrey, I hate to do this. Let's put the balance of your statement—or do you have much more of it?

Mr. LAUGHREY. Well, I do have a chart that I wanted to reference here. I noted that when Mr. Mossinghoff was here you did reference this. If I could just address that chart, sir.

The CHAIRMAN. Yes.

Mr. LAUGHREY. This is a pricing pattern of a typical—

The CHAIRMAN. Now, are we talking about the patent expiration chart?

Mr. LAUGHREY. Yes. The chart on the left, before and after patent expiration.

The CHAIRMAN. All right.

Mr. LAUGHREY. Now, the pricing pattern of drug X represents the classic pattern seen for many originator drug products as they go off patent. Brand A of drug X has its first generic competition from generic C in mid-1985. Despite the introduction of lower cost therapeutically equivalent products, such as generic C or generic D, brand A continued to increase AWP at about the same rate as it did when the product was patent protected. Generic B had set its price just under brand A at the time of the market entry, and has since held that price constant. Generic C and D appear to have been engaged in competitive behavior; even though only four products are shown for drug X in figure 4, there were actually more than 35 companies marketing an FDA-rated therapeutic equivalent drug product.

Now, we do have other examples.

The CHAIRMAN. Well, let me ask, Mr. Laughrey, on generic B, on the blue line, that's a new generic drug to compete with brand A, right?

Mr. LAUGHREY. Yes, sir.

The CHAIRMAN. Am I not mistaken, though, isn't generic B drug produced by the same company that makes brand A? In other words, they've made their own generic to compete with their own brand drug, is this correct?

Mr. LAUGHREY. I don't have knowledge that that is correct. That's a postulation that could possibly occur.

Mr. LAUGHREY. If I could just summarize, sir.

The CHAIRMAN. Yes, sir. Because we are out of time and we're going to move rapidly.

Mr. LAUGHREY. Well, in summary, many drug companies appear to continue pricing their off-patent product in much the same way as they priced that product as a single source agent. Even when a number of generic products have come into the market and offer prices that are considerably below the original brand price, many drug companies continue to hold, or even raise, the AWP of their multiple source product similar to that of a single source product. This general statement must be viewed with caution, however, since there are certain brand name manufacturers in certain therapeutic categories where the brand name product is quite competitive in the multiple source market.

[The prepared statement of Mr. Laughrey follows:]

TESTIMONY OF
J. BRUCE LAUGHREY, PRESIDENT
MEDI-SPAN, INC.
TO UNITED STATES SENATE
THE SPECIAL COMMITTEE ON AGING
DAVID PRYOR, CHAIRMAN
TUESDAY, JULY 18, 1989

Mr. Chairman, my name is J. Bruce Laughrey, President of Medi-Span, Incorporated of Indianapolis, Indiana. Medi-Span is a privately-held corporation whose primary business is the collection of data and publishing of information concerning pharmaceuticals for the health-care industry. Our customers include retail pharmacists, drug chains, manufacturers, wholesalers, insurers, third party administrators, HMO's, hospitals, and physicians. We are pleased to accept this invitation to testify before this committee and to share information concerning pharmaceutical pricing trends.

Medi-Span's Prescription Pricing Guide, first published in 1977, is a monthly publication listing Average Wholesale Price (AWP) and manufacturer's Direct Prices (DP) for approximately 6,000 of the most commonly used prescription pharmaceuticals (See Figure 1). Over the past twelve years, Medi-Span has introduced a variety of printed publications as well as expanded into providing computerized databases of pharmaceutical information in electronic media to support numerous computerized applications. Today, Medi-Span's MASTER DRUG DATA BASE (MDDB) a core file of information contains current as well as historic price information on over 100,000 pharmaceutical and health related products in the United States market.

The published Average Wholesale Price, or AWP, is a key index price included in both our print and electronic publications. This AWP is widely accepted and used in the industry as the basis for the purchase of drug products. In addition, many third party payers of prescription insurance benefits reimburse pharmacists on the basis of a professional fee plus the cost of medication provided. The published AWP is used as the cost component in this reimbursement formula.

The published AWP is obtained directly from over 600 pharmaceutical manufacturers, distributors and wholesalers. We validate the information published by using multiple information sources where feasible.

We would like to clarify that the published AWP is a standard reference price and does not recognize earned discounts for quantity purchases, bid or contract pricing or other forms of trade discounts. Thus, the AWP is the price that the pharmacy would typically pay if they purchased a single bottle of the item from a local drug wholesaler. The published AWP remains the only consistent index price that is useful for comparative purposes.

Much of the comparative Average Wholesale Price information we were requested to provide is included in one of our publications, the Generic Buying and Reimbursement Guide (GBRG) (Sample page Figure 2). The GBRG is a quarterly publication, subscribed to by thousands of pharmacies, as an aid in selecting the most economical therapeutic equivalent product available in the marketplace. By including the Average Wholesale Price (AWP) information along with the FDA therapeutic equivalence evaluation ode ("Orange Book" rating), product selection and buying decisions are greatly enhanced.

The invitation to testify asked us to examine the pricing patterns of a specific set of drugs by referring to the AWP histories maintained in our MASTER DRUG DATA BASE (MDDB). This set of ten single-source items frequently used by the elderly, were found to have increased AWP at an average annual rate of 9.2 percent between January 1, 1982 and December 31, 1986 (Table 1). This same set of single-source drugs averaged a 7.9 percent AWP increase in 1987 and a 9.0 percent AWP increase during 1988.

A set of thirty-five multiple-source drugs, frequently used by the elderly, was also examined to determine AWP changes between 1982 and 1988. The originator brands of these multiple-source drugs had an average annual AWP price increase of 9.9 percent between 1982 and 1986 (Table 2). In 1987, the average annual AWP increase was 6.9 percent, and in 1988 AWP increased by 6.4 percent for the originator brands of this group of multiple source drugs.

Not all of the multiple-source drugs were off patent during the entire period of 1982 to 1986. More than one-third of the drugs in this group were still under patent protection for at least part of the period 1982 to 1986. It is noteworthy that the originator brands in both the single-source drug group and the multiple-source drug group had similar annual rates of increase in AWP between 1982 and 1986 with increases of 9.2% and 9.9% respectively (Figure 3). It appears that, in general, single-source drugs in the period just prior to patent expiration do not experience a slowed, or declined, rate of AWP increases, but rather the AWP changes continue for these products at rates similar to single-source products (Figure 3).

Once drug products have been off patent for several years, their rate of AWP increase does appear to moderate somewhat with respect to the rate of increase in AWP for single-source products. (Figure 3). Originator brands of multiple-source drugs had lower annual AWP increases than single-source drugs in both 1987 and 1988.

Originator brand products tend to continue AWP price increases at about the same, or slightly lower, rates as when the product was patent protected. This trend persists despite the fact that generic products may be introduced into the market and may experience significant competition and decreases in AWP prices.

The price change patterns of all brand name manufacturers should not be painted with a single broad brush. In examining changes in AWP over time as products go off patent, one notes patterns unique to specific drug companies and to specific drug therapy categories. During 1987, for example, eleven of the thirty-five originator brands of multi-source drugs had no increase in AWP, while another seven of the thirty-five had increases of 10 percent or more (Table 3).

Actual pricing patterns for therapeutically equivalent versions of four multiple-source drug products are illustrated in Figures 4 through 7. These figures are case studies presented only for the purpose of showing typical patterns of actual pricing behavior, not to highlight the pricing decisions of a particular company.

The pricing pattern of Drug X (Figure 4) represents the classic pattern seen for many originator drug products as they go off patent. Brand A of Drug X has its first generic competition from Generic C in mid-1985. Despite the introduction of lower cost, therapeutically equivalent products such as Generic C or Generic D, Brand A continued to increase AWP at about the same rate as it did when the product was patent protected. Generic B had set its price just under Brand A at the time of market entry and has since held that price constant. Generic C and D appear to have been engaged in competitive behavior. Even though only four products are shown for Drug X in Figure 4, there are actually more than 35 companies marketing and FDA "A" rated therapeutically equivalent drug product.

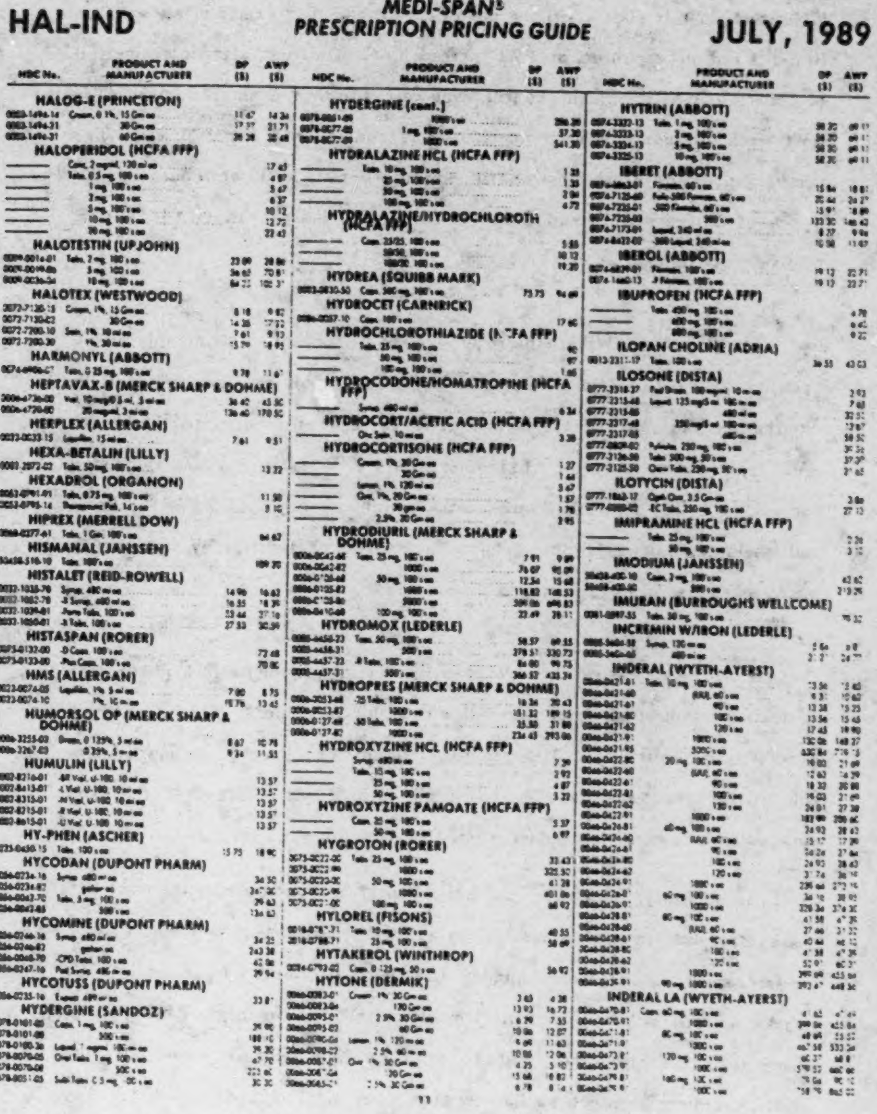
Drug Y (Figure 5) and Drug Z (Figure 6) exhibit patterns similar to Drug X as previously discussed. These additional cases are included to show typical variations in this classic pricing pattern. Drug Z, for example, shows that Brand A did not announce an AWP increase in the first year after introduction of generic competition. In the following year, however, Brand A increased its AWP even though generic competitors had considerably lower prices. The company of Brand A has since continued increasing its AWP while generic AWP prices of Generics C, D, and E appear to have leveled off and are in a fairly narrow price range.

The Brand A AWP in the Drug X, Y, and Z cases is considerably higher than the lowest generic price. The range of prices can be compared by determining the ratio of the highest AWP for a drug product to the lowest AWP for the same product. This high to low AWP ratio has been calculated for each of the multiple-source drug product groups (Table 4). Some multiple-source drug product groups have AWP's that differ by high-to-low ratios as high as 20 to 1, or even 32 to 1.

Drug Q (See Figure 7) provides an interesting pricing pattern in contrast to the more typical patterns observed with Drugs X, Y, and Z. The high-to-low ratio is only about 2 to 1, indicating that Brand A of Drug Q was more "price competitive" than was Brand A of Drugs X, Y, or Z. Also, Brand A of Drug Q appears to have extended the length of time between price increases.

In summary, many drug companies appear to continue pricing their off-patent product in much the same way as they priced that product as a single-source agent. Even when a number of generic products have come into the market and offer prices that are considerably below the original brand price, many drug companies continue to hold or even raise the AWP of their multiple-source product similar to that of a single-source product. This general statement must be viewed with caution, however, since there are certain brand name manufacturers and certain therapeutic categories where the brand name product is quite competitive in the multiple-source market.

FIGURE 1



HAL-IND

MEDI-SPAN PRESCRIPTION PRICING GUIDE

JULY, 1989

NDC No. | PRODUCT AND MANUFACTURER | DP ($) | AWP ($)

HALOG-E (PRINCETON)

HALOPERIDOL (HCFA FFP)

HALOTESTIN (UPJOHN)

HALOTEX (WESTWOOD)

HARMONYL (ABBOTT)

HEPTAVAX-B (MERCK SHARP & DOHME)

HERPLEX (ALLERGAN)

HEXA-BETALIN (LILLY)

HEXADROL (ORGANON)

HIPREX (MERRELL DOW)

HISMANAL (JANSSEN)

HISTALET (REID-ROWELL)

HISTASPAN (RORER)

HMS (ALLERGAN)

HUMORSOL OP (MERCK SHARP & DOHME)

HUMULIN (LILLY)

HY-PHEN (ASCHER)

HYCODAN (DUPONT PHARM)

HYCOMINE (DUPONT PHARM)

HYCOTUSS (DUPONT PHARM)

HYDERGINE (SANDOZ)

HYDERGINE (cont.)

HYDRALAZINE HCL (HCFA FFP)

HYDRALAZINE/HYDROCHLOROTH (HCFA FFP)

HYDREA (SQUIBB MARK)

HYDROCET (CARNRICK)

HYDROCHLOROTHIAZIDE (HCFA FFP)

HYDROCODONE/HOMATROPINE (HCFA FFP)

HYDROCORT/ACETIC ACID (HCFA FFP)

HYDROCORTISONE (HCFA FFP)

HYDRODIURIL (MERCK SHARP & DOHME)

HYDROMOX (LEDERLE)

HYDROPRES (MERCK SHARP & DOHME)

HYDROXYZINE HCL (HCFA FFP)

HYDROXYZINE PAMOATE (HCFA FFP)

HYGROTON (RORER)

HYLOREL (FISONS)

HYTAKEROL (WINTHROP)

HYTONE (DERMIK)

HYTRIN (ABBOTT)

IBERET (ABBOTT)

IBEROL (ABBOTT)

IBUPROFEN (HCFA FFP)

ILOPAN CHOLINE (ADRIA)

ILOSONE (DISTA)

ILOTYCIN (DISTA)

IMIPRAMINE HCL (HCFA FFP)

IMODIUM (JANSSEN)

IMURAN (BURROUGHS WELLCOME)

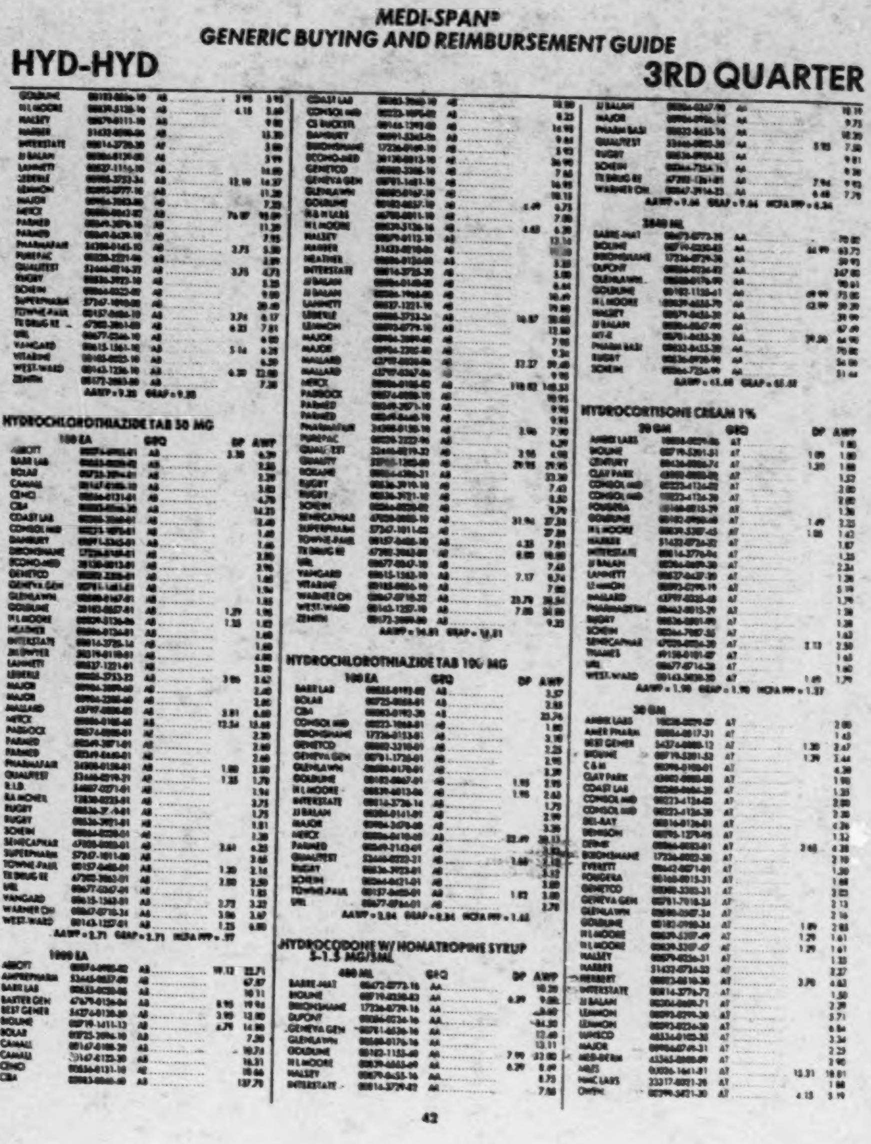
INCREMIN W/IRON (LEDERLE)

INDERAL (WYETH-AYERST)

INDERAL LA (WYETH-AYERST)

11

FIGURE 2



MEDI-SPAN®
GENERIC BUYING AND REIMBURSEMENT GUIDE

HYD-HYD

3RD QUARTER

HYDROCHLOROTHIAZIDE TAB 50 MG

100 EA

1000 EA

HYDROCHLOROTHIAZIDE TAB 100 MG

100 EA

HYDROCODONE W/ HOMATROPINE SYRUP 5-1.5 MG/5ML

480 ML

3840 ML

HYDROCORTISONE CREAM 1%

20 GM

30 GM

42

TABLE 1. Average Annual Price Changes for Selected Single Source Drugs Used By the Elderly: 1982-1988

SINGLE SOURCE DRUG

			Most Frequently Purchased			Annual % Price Increase		
Brand Name	Generic Name	Manuft.	Dosage Form	Strength	Pkg Size	1-1-82 to 1-1-87	1-1-87 to 1-1-88	1-1-88 to 1-1-89
Tenormin	Atenolol	Stuart	tablets	50 mg	100s	9.5	13.9	5.0
Timoptic	Timolol	MSD	ophth. soln.	0.5 mg	10 ml	5.5	4.0	6.0
Naprosyn	Naproxen	Syntex	tablets	375 mg	100s	7.9	7.1	5.0
LoPressor	Metaprolol	CIBA -Geigy	tablets	50 mg	100s	15.0	12.1	28.2
Feldene	Piroxicam	Pfizer	capsules	20 mg	100s	--	9.8	9.8
Procardia	Nifedipine	Pfizer	capsules	10 mg	300s	9.2	9.8	9.9
Cardizem	Diltiazem	Marion	tablets	60 mg	100s	6.6	6.0	0.0
Capoten	Captopril	Squibb	tablets	25 mg	100s	7.2	9.2	10.4
Zantac	Ranitidine	Glaxo	tablets	150 mg	60s	10.8	7.3	6.0
Tagament	Cimetidine	SKF	tablets	300 mg	100s	11.5	0.0	10.0
Single Source Average						9.2	7.9	9.0

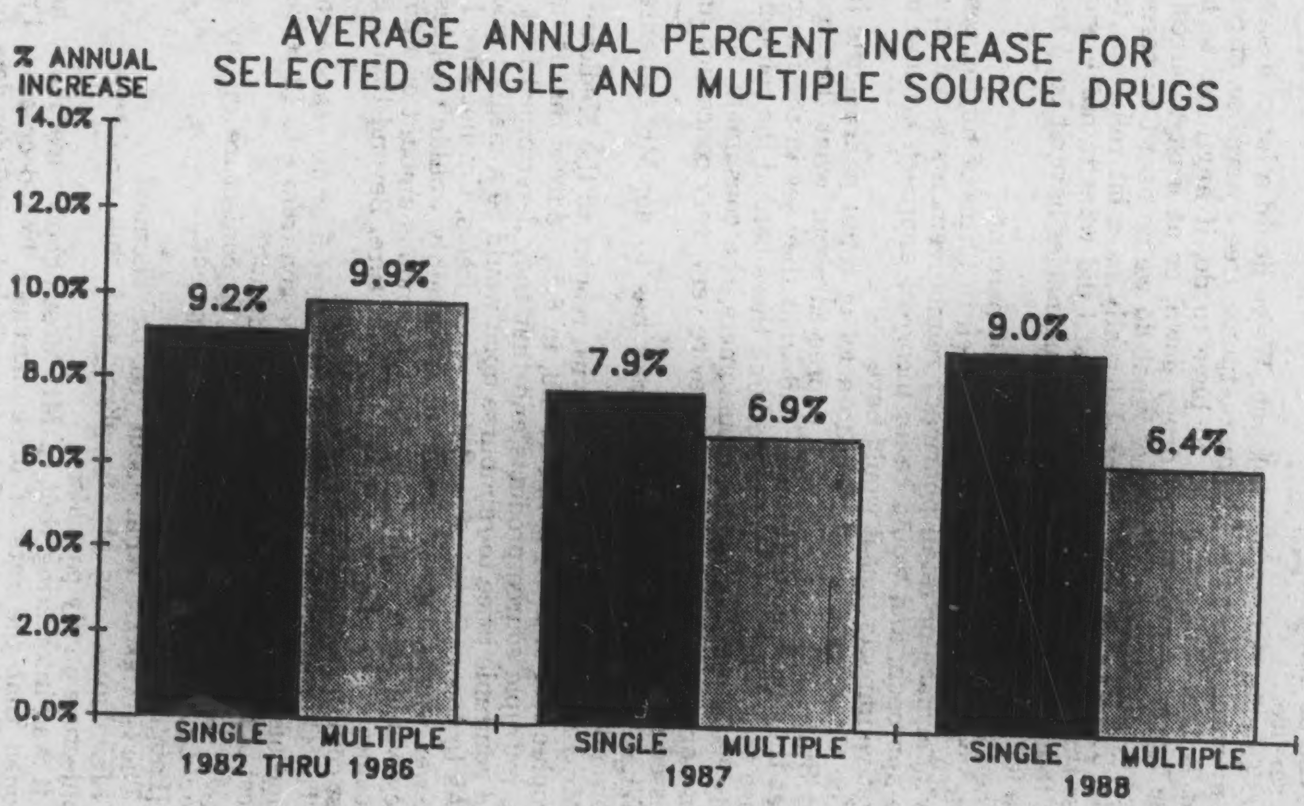
TABLE 2. Average Annual Price Change for Selected Multiple Source Drugs Frequently Used By the Elderly: 1982-1988

MULTIPLE SOURCE DRUG			Most Frequently Purchased			Annual % Price Increase		
Brand Name	Generic Name	Manufacturer	Dosage Form	Strength	Pkg Size	1-1-82 to 1-1-87	1-1-87 to 1-1-88	1-1-88 tc 1-1-89
Dyazide	Triamterene and Hydrochlorothiazide	SKF	capsules	50 mg/ 25 mg	1000s	13.5	31.0	9.4
Isordil	Isosorbide Dinitrate	Ives	tablets	10 mg	100s	10.2	23.0	0.0
Micro-K	Potassium Chloride	Robins	SR caps.	10 mg	100s	--	4.8	11.1
Fluogen	Influenza Virus Vaccine	Parke-Davis and others	inject	--	5 ml	--	0.0	0.0
Lasix	Furosemide	Hoechst	tablets	40 mg	100s	2.0	0.0	8.0
Inderal	Propranolol	Wyeth-Ayerst	tablets	40 mg	100s	18.2	0.0	10.0
Hydrodiuril	Hydrochlorothiazide	MSD	tablets	50 mg	100s	13.2	6.8	9.6
Rufen	Ibuprofen	Boots	tablets	800 mg	100s	--	0.0	5.2
Motrin	Ibuprofen	Upjohn	tablets	800 mg	100s	0.0	0.0	0.0
Deltasone	Prednisone	Upjohn	tablets	5 mg	500s	1.6	5.0	-52.6
Aldomet	Methyldopa	MSD	tablets	250 mg	100s	12.2	6.8	9.5
Bactrim DS	Trimethoprim/Sulfamethoxazole	Roche	tablets	160 mg/ 800 mg	100s	9.5	9.9	9.9
Septra DS	Trimethoprim/Sulfamethoxazole	BW	tablets	160 mg/ 800 mg	100s	7.7	19.8	9.9
Diabenese	Chlorpropamide	Pfizer	tablets	250 mg	100s	7.3	9.3	9.1
Theo-DUR	Theophylline	Key	SR tabs	300 mg	100s	9.9	0.0	0.0
Keflex	Cephalexin	Lilly/Dista	capsules	500 mg	100s	12.6	5.0	7.0
Antivert	Meclizine HCl	Roerig	tablets	25 mg	100s	13.6	9.7	9.7

TABLE 2. (Continued)

MULTIPLE SOURCE DRUG			Most Frequently Purchased			Annual % Price Increase		
Brand Name	Generic Name	Manufacturer	Dosage Form	Strength	Pkg Size	1-1-82 to 1-1-87	1-1-87 to 1-1-88	1-1-88 to 1-1-89
Darvocet N	Propoxyphene Napsylate/ Acetaminophen	Lilly	tablets	100 mg/ 650 mg	500s	--	9.0	9.0
Indocin	Indomethacin	MSD	capsules	25 mg	100s	13.2	6.8	9.5
AchromycinV	Tetracycline HCl	Lederle	capsules	250 mg	100s	5.2	5.0	4.9
Aldoril	Methyldopa/Hydro- chlorothiazide	MSD	tablets	25 mg	100s	--	6.8	9.5
Maxitrol	Dexamethasone/ polymyxin B sulfate/neomycin sulfate	Alcon	ophth. suspn	0.1 % 6000 un. 3.5 mg	5 cc	10.1	6.6	6.3
Valium	Diazepam	Roche	tablets	5 mg	500s	16.6	10.0	15.1
Zyloprim	Allopurinol	BW	tablets	300 mg	100s	6.0	0.0	9.0
Ativan	Lorazepam	Wyeth-Ayerst	tablets	1 mg	100s	18.1	0.0	12.0
Tolinase	Tolazamide	Upjohn	tablets	250 mg	100s	8.0	0.0	0.0
E-Mycin	Erythromycin Base	Upjohn	EC tabs	333 mg	100s	1.8	0.0	38.9
Polycillin	Ampicillin	Bristol	capsules	500 mg	100s	0.0	5.0	0.0
Amoxil	Amoxicillin	Beecham	tablets	500 mg	100s	0.0	0.0	0.0
Hygroton	Chlorthalidone	Rorer	tablets	50 mg	100s	8.2	12.0	12.5
Elavil	Amitriptyline	MSD	tablets	25 mg	100s	18.5	6.8	9.5
Lanoxin	Digoxin	BW	tablets	0.25 mg	1000s	31.9	9.8	7.0
Persantine	Dipyridamole	Boehringer Ingelheim	tablets	50 mg	100s	5.2	6.0	6.0
Synthroid	Levothyroxine Sodium	Flint	tablets	0.1 mg	100s	20.5	12.9	13.4
Trans Derm Nitro	Nitroglycerin	CIBA-Geigy	trans-derm patch	5 mg	30s	1.4	5.0	5.5
Multiple Source Average						9.9	6.9	6.4

FIGURE 3



AVERAGE ANNUAL PERCENT INCREASE FOR SELECTED SINGLE AND MULTIPLE SOURCE DRUGS

The **CHAIRMAN.** I really want to thank you. I sat up last night and read as much as I could about Medi-span and it is a very valuable service.

Dr. Thomas, let me just ask you. We've heard a lot of discussion this morning about the free marketplace, free enterprise, et cetera, what is the Congress going to have to do, if anything, to bring these prices of prescription drugs down, or at least to arrest the very rapidly increasing prices. What do we do as a Congressman?

Mr. **THOMAS.** Senator Pryor, I'd really be a bit reluctant to address that. I mean, the one point that I did want to make was the fact that pharmacists, community pharmacies haven't been responsible for the increase.

The **CHAIRMAN.** I agree with you 100 percent.

Mr. **THOMAS.** And that the approach in terms of hitting community pharmacy or retail pharmacy reimbursements is not an effective approach, and would be an incorrect approach because of the negative impacts that it would have.

The **CHAIRMAN.** I've talked to a lot of retail pharmacists in my own State and they are very depressed about what they see and what they have gone through, and what they see in the future, because they see no let up for standing there behind the counter on a daily basis and telling their customers, the consumers, that their drugs are going up again. And they're very, very concerned and depressed about this.

What do you think the Congress has to do, Mr. Laughrey? Is there anything we can do?

Mr. **LAUGHREY.** Well, I think, with respect to the Medicare Catastrophic Act of 1987, Congress did, in fact, address that issue with the multiple source products and that they determined that a fair and equitable price to reimburse upon would be a median price.

As to the patented prescription drug items, I'm not sure I could answer what Congress should do. I certainly wouldn't suggest that they would deter in any way the tremendous amount of innovation that occurs in pharmaceutical manufacture. Beyond that I guess I just couldn't comment, sir.

The **CHAIRMAN.** Do you see, in the next 5 or 10 years a continuation of our chart going up each year, say, from 8 to 12 percent, on most of our drugs? Is this going to continue?

Mr. **LAUGHREY.** Well, that would be conjecture on my part. I would guess after this hearing, perhaps not.

[Laughter.]

The **CHAIRMAN.** What about you, Dr. Thomas?

Mr. **THOMAS.** As Mr. Laughrey said, that would really be just conjecture on my part also.

It was interesting that in Mr. Mossinghoff's testimony he mentioned that the rate of price increases had decreased. I'm sure you'll be watching carefully to see what trend develops over the next couple of years.

The **CHAIRMAN.** As my colleagues left the room this morning one of them whispered over to me, he says, I see the problem, now what's the solution? And we're going to be at that stage, and that's going to be part of what we're going to be talking about at our next hearing.

Were you surprised, either one of you—let's put the international drug pricing chart back up—were you surprised to see that particular chart showing how much more Americans pay for the same drugs as our European friends? Did this surprise either one of you? Dr. Thomas.

Mr. **THOMAS**. I have to say the extent of the range in the prices was a bit surprising to me. The fact that there was quite a bit of diversity was not a surprise. I was aware of that. But the range was a bit surprising.

The **CHAIRMAN**. By the way, in the past I think the pharmaceutical manufacturers have maintained it is impossible to accurately reflect the data in this chart. I don't know what kind of analytical data this is or how valid it is, but I know that the Italian pharmaceutical manufacturers association did this particular workup. That's where we got it, and that's the best I've ever seen in comparing our prices to some of the European prices.

What about you, Mr. Laughrey, were you surprised at this?

Mr. **LAUGHREY**. I guess not. I've known that there have been price disparities internationally. But then again, I believe that perhaps a socialistic country might buy in bulk, and achieve a quantity discount.

The **CHAIRMAN**. Well, we're talking about the same pharmaceuticals that are sold here that are sold there. Do you think the bulk buying would reflect that sort of a variation? I would have trouble finding that.

Mr. **LAUGHREY**. Well, our company doesn't track international pricing. If in fact that chart is correct, it's a little surprising.

The **CHAIRMAN**. Does it also maybe surprise you a little bit, or would you have any comment on the fact that we give them R&D tax credits, the opportunity to manufacture in Puerto Rico with no taxes under Section 936, an exemption in State sales tax and other taxes for them to locate in some States, and even with all of that, give them a patent for 17 years, and they sell these drugs so much more cheaply in other countries than they sell them in this country? Does that do anything to you?

Mr. **LAUGHREY**. It doesn't sound inconsistent with our other economic policies worldwide, sir.

The **CHAIRMAN**. Maybe that's why we're in such a mess.

Dr. Thomas, do you have any comments on that?

Mr. **THOMAS**. Not on that. If I could go back to one of your earlier questions, I'd like to comment.

The **CHAIRMAN**. Yes.

Mr. **THOMAS**. In terms of what you were asking; what we could do in controlling prescription drug expenditure increases, I think you do have to look at the expenditures as well as the prices. One of the things that I would like to see in terms of developing a prescription drug program benefit is that we provide some positive incentives to pharmacists for some of the activities that they perform that improve and lower total program costs. For example, when a pharmacist takes action in terms of identifying a drug interaction, or identifying that a patient is on duplicate drug therapy, and calls the physician and persuades the physician that no drug is needed. The pharmacist doesn't get any reimbursement for that. The pharmacist has no positive incentive to perform that type of activity, except based on his role as a professional.

The CHAIRMAN. Right.

Mr. THOMAS. I think we do need to gather some additional data to understand better the factors behind the increases in drug prices. As we've seen here today, it's a very complex issue. And changes in one part of the system have consequences in other parts of the system that we may not actually be looking at as we effect those. So I think it's obvious that there is a need for gathering much more data.

The CHAIRMAN. Yes, sir.

Mr. THOMAS. One other point, and that's that we need to really develop some data so we understand the relationship, something that Mr. Mossinghoff mentioned, the relationship between expenditures on drugs and other medical expenditures.

The CHAIRMAN. All right.

Let me ask you this question. Were you surprised earlier this morning, if you were here, when you saw that Medicare pays so much more for their drugs that they buy than the Veterans Administration, like $29 to $5?

Mr. THOMAS. I have to say that I was not.

The CHAIRMAN. You were not surprised?

Mr. THOMAS. I was not.

The CHAIRMAN. Why were you not surprised?

Mr. THOMAS. Being aware of the fact that the system that the Veterans Administration operates on versus the system that Medicaid system works on, they really are two different systems. And Medicaid ends up paying the prices that pharmacists pay to obtain those drugs.

The CHAIRMAN. I know, but it all comes out of the same pocket, doesn't it?

Mr. THOMAS. It does come out of the same pocket, but given the fact that there are two different systems and the way that those systems operate, I was not surprised.

The CHAIRMAN. What would you think about letting the Veterans Administration become the buyer of prescription drugs for the U.S. Government? Let them do all the Medicaid, and all the Medicare purchasing. What would you think of that?

Mr. THOMAS. I think there are some things that have to be considered before I'd move in that direction. First of all, the Veterans Administration can act as a depot system because of the number of final distribution centers that are involved. Community pharmacies really are the most accessible form of health care for patients. It would be very difficult with a depot system to administer a type of program that would function and provide those drugs to those pharmacies. It would be very expensive on an administrative basis.

The CHAIRMAN. We're just trying to find the answers.

Mr. THOMAS. There may be other avenues that take advantage of some of the things that the Veterans Administration does.

The CHAIRMAN. If you know of those avenues, would you please write me a letter, or call me up, because we're looking for those answers.

Mr. THOMAS. I would be glad to explore those with you.

The **Chairman.** Mr. Laughrey, do you have any comments on that final line of questioning?

Mr. **Laughrey.** Well, the product in question was Motrin. It has lost its patent, it is now available as a multiple source product, so it didn't surprise me that in fact the VA hospitals could receive a $5 price as opposed to the $29 price that Medicare might pay. Single source items, it might be a little more difficult to negotiate those types of discounts given our retail pharmacists' distribution system.

The **Chairman.** Do you think that Medicare should attempt to negotiate with the vendors, just like the Veterans Administration has?

Mr. **Laughrey.** I think they should attempt to. Obviously, if we can save our taxpayers' money——

The **Chairman.** Watching trends in drug prices, would you have any faith or any reason to believe that the drug manufacturers would want to negotiate with Medicare, just as some of them might have with the Veterans Administration?

Mr. **Laughrey.** I would guess they would prefer not to negotiate.

The **Chairman.** Why?

Mr. **Laughrey.** I think they want to continue their level of profitability as they have in the past.

The **Chairman.** Which has been relatively or extremely high?

Mr. **Laughrey.** Well, that's a postulation again on my part. I'd say it's reasonably high.

The **Chairman.** OK, sir.

I want to thank both of you. You've been very constructive this morning, and again, very patient. And we're going to put your full statements in the record, and we'll perhaps be calling on you again for your expertise and your knowledge, and certainly your cooperation.

We have Mr. Louis Hays. Mr. Hays, we welcome you today. I don't know if you had to sit through all of this this morning, but we've had a very lively discussion on prescription drug prices, costs, value, et cetera. And we look forward to your statement. We're going to try to limit this statement to 5 minutes, and then I will have a few questions, not many. But we appreciate you coming, and appreciate your statement. The full body of your statement will be printed in the record.

STATEMENT OF LOUIS B. HAYS, ACTING ADMINISTRATOR OF HCFA, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. **Hays.** Thank you very much, Mr. Chairman. I am pleased to be here today to discuss the pricing of outpatient prescription drugs under the Medicare Program.

At the outset, let me reiterate that our estimates of the Medicare outpatient prescription drug program continue to show that the program is considerably underfunded. Over the first 4 years of the program, benefits are expected to exceed the premiums received by nearly $800 million, and with administrative costs included, the shortfall rises to almost $2.8 billion. I understand that the most recent Congressional Budget Office projections are consistent now with the administration's projections.

With respect to the drug pricing mechanism under the new drug program, the law is very specific with regard to Medicare payments for outpatient prescription drugs. After the annual deductible is met, Medicare will pay the lesser of the pharmacy's actual charge for the drug, or an applicable payment limit minus the required coinsurance amount. The payment limit depends on whether the drug is available from multiple sources, only a single source, or as a brand name drug specified in writing by the physician. The payment limit for most drugs will be average wholesale price of the drug. While the term "average wholesale price" is suggestive of the amount that pharmacies actually pay for drugs, it is in fact, significantly higher than actual costs. The average wholesale price is somewhat comparable to the manufacturer's sticker price on a new car.

Indeed, there have been a number of studies which indicate that published average wholesale price for drugs overstates the actual prices paid by as much as 10 to 20 percent, because of discounts, special offers, or purchasing incentives. Unlike the Medicaid Program, we have no authority to take advantage of these discounts under Medicare.

You specifically asked that I mention our decision on the newly approved drug, Epoetin, otherwise known as EPO. On June 1, the Food and Drug Administration approved Epoetin for the treatment of anemia associated with chronic renal failure. This drug is expensive, and since the Medicare Program pays the vast majority of expenses for end-stage renal disease patients, we held significant discussions with the company that received FDA approval for the drug, namely, Amgen Inc. Based on those discussions, which included examination of detailed cost data volunteered by Amgen, we set a reasonable price to pay kidney-dialysis facilities for the administration of this drug in conjunction with dialysis treatment. The price we announced is $4,650 for each person receiving Epoetin. We plan to evaluate the price in 6 months, but we believe the price we set is reasonable for both dialysis facilities and the taxpayer.

The Department has been concerned with the cost of the outpatient prescription drug program since discussions of the benefit began over 2 years ago. In a May 1989 report to Congress we outlined the assumptions used in calculating the $2.8 billion deficit in the drug trust fund. We estimate that Medicare beneficiaries who purchased prescriptions in 1988 purchased an average of 21.5 prescriptions in that year. By 1993, that figure will rise to 23.3 prescriptions. We also estimate that the average cost for outpatient prescription drugs will increase from $18.21 in 1988 to $24.26 by 1993. Finally, we assume an induced demand effect which could increase aggregate consumption of drugs by the Medicare population by about 10 percent in 1991, 12 percent in 1992, and 11 percent in 1993.

We are also preparing a report to Congress on drug prices and pharmacy charges as required by the catastrophic legislation. Allow me to describe briefly some of the trends that we will be mentioning in our report.[9]

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[9] See appendix 3 draft report to Congress on Manufacturers' Prices and Pharmacists' charges.

The producer price index measures the change over time in the prices received in commercial transactions by manufacturers and producers of various goods. In the case of prescription drugs, the producer price index, or PPI, is a measure of the change in prices charged by drug manufacturers for the drugs they sell. Between 1981 and 1986 the annual growth rate in the PPI for prescription drugs was 10.1 percent. In 1987 and 1988 the PPI moderated somewhat to 9.6 percent and 7.9 percent respectively. Similar trends have been noted in the growth of the consumer price index for drugs as well.

In concluding my statement, Mr. Chairman, I would note that the catastrophic drug benefit represents a major expansion of the Medicare Program, and presents us with enormous administrative challenges. As we proceed with implementation, on schedule, we are concerned by the projected underfunding of the drug trust fund and the volatility of prescription drug prices in recent years. We look forward to working with this committee, and the others in the Congress, to help ensure that the drug program is financially sound, and that it serves Medicare beneficiaries well. I would be happy to answer any questions that you might have, Mr. Chairman.

[The prepared statement of Mr. Hays follows:]

STATEMENT OF LOUIS B. HAYS
ACTING ADMINISTRATOR
HEALTH CARE FINANCING ADMINISTRATION
BEFORE
THE SPECIAL COMMITTEE ON AGING
UNITED STATES SENATE
JULY 18, 1989

Good morning. I am pleased to be here today to discuss the pricing of outpatient prescription drugs under Medicare.

At the outset, I must reiterate, as stated in our May 1989 Report to Congress concerning the catastrophic outpatient drug program, that HCFA estimates of the Medicare outpatient drug program continue to show that the program is considerably underfunded. Over the first four years of the program (1990 - 1993), benefit payments are expected to exceed premiums received by nearly $800 million. With administrative costs included, the shortfall rises to almost $2.8 billion. I understand that the most recent Congressional Budget Office (CBO) projections are consistent with the Administration's projections. By the end of 1992, we project that there will be insufficient cash on hand in the Catastrophic Drug Insurance Trust Fund to pay claims, and some benefit payments will have to be deferred until additional premiums come in.

With the financial difficulty facing the drug trust fund as a sobering reminder of our responsibility to foster the drug program's viability, allow me to share with you an explanation of the new drug benefit and its financing mechanism, as well as information on the trends in prescription drug costs over the past several years.

THE MEDICARE OUTPATIENT DRUG BENEFIT

The outpatient prescription drug program under Medicare is intended to help relieve the financial burden sometimes imposed on beneficiaries by unusually high outpatient prescription drug bills. This new benefit represents a significant expansion of Medicare. Beginning in 1990, Medicare will pay for drugs used in immunosuppressive therapy and certain home intravenous (IV) drugs. In 1991, the benefit will expand to include all other outpatient prescription drugs approved by the Food and Drug Administration (FDA).

After a beneficiary has satisfied an annual deductible, Medicare will pay its share of the cost of a particular drug, and the beneficiary will be responsible for the remainder, a so-called coinsurance amount. With some exceptions, the coinsurance amount is 50 percent in 1991, 40 percent in 1992, and 20 percent in 1993 and thereafter (providing the required contingency margin for the Catastrophic Drug Insurance Trust Fund is met).

OUTPATIENT PRESCRIPTION DRUG PRICING UNDER MEDICARE

The law is very specific with regard to Medicare payments for outpatient prescription drugs. After the annual deductible is met, Medicare will pay the lesser of the pharmacy's actual charge for the drug, or the applicable payment limit, minus the required coinsurance amount. The method Medicare must employ in calculating payment limits is set in law. While it is a rather detailed methodology, allow me to briefly mention key aspects of it to give you a flavor for the very explicit and inflexible nature of the methodology. It is readily apparent that very little, if any, opportunity exists within this payment framework to encourage cost savings in the outpatient drug program.

The methodology for calculating Medicare's payment for a drug depends on whether the drug is available from multiple sources, only a single source, or is a brand name drug specified in writing by the physician.

For single source drugs and multiple source drugs with brand names prescribed: Prior to January 1, 1992, the payment limit is the number of units dispensed multiplied by the per unit average price for the drug, plus an administrative allowance. Beginning January 1, 1992, the payment limit is the lesser of the calculation specified above or the 90th percentile of the actual charge per unit computed on a geographic basis for the second previous calculation period, adjusted to reflect the number of units dispensed.

For multiple source drugs: The payment limit is the number of units dispensed multiplied by the average price per unit plus the administrative allowance.

To determine the average price of single source drugs, the Secretary is required to conduct a biannual survey of direct sellers, wholesalers, or pharmacies as appropriate. If the sales volume of a drug is so low that such a survey is not appropriate, or for other reasons, the Secretary may price the drug based only on the published average wholesale price.

To determine the average price of multiple source drugs, the Secretary may price the drug based on either the published average wholesale price or the biannual survey.

Even while I have spared you many of the details and nuances of the law, it is clear that HCFA has little room to innovate within this rigid payment system. Under current law, HCFA has no authority to negotiate more competitive prices or demand the discounts warranted by the large volume of business the Medicare program represents. Indeed, the statute requires us to exclude from the price survey the discounts which pharmacies typically receive from drug companies. Thus, the survey prices will overstate actual pharmacy costs. Multiple source drugs make up the lion's share of the prescription drug market, and, essentially, Medicare will pay the average wholesale price for these drugs. While the term "average wholesale price" is suggestive of the amount that pharmacies actually pay for drugs, it is significantly higher than actual costs. The average wholesale price is somewhat comparable to the manufacturer's "sticker price" on a new car -- this is rarely the price actually paid for the car. Indeed, there have been a number of studies which indicate that the published average wholesale price for drugs overstates actual prices paid by as much as 10 to 20 percent because of discounts, special offers or purchasing incentives.

The states have had more than 20 years of experience paying for prescription drugs under the Medicaid program. Many states have employed creative and cost effective methods of limiting their drug costs without lowering the quality of care. For example, the state of Maine pays the average wholesale price minus 5 percent, while both Tennessee and Ohio pay the average wholesale price minus 7.5 percent. To further illustrate, South Carolina pays the average wholesale price minus 9.5 percent, and Texas pays the average wholesale price minus 10.5 percent. These reductions from the average wholesale price are usually based on surveys, conducted by states, of dispensing costs and actual acquisition costs for pharmacies.

EPOETIN

You specifically asked that I mention our decision on the newly approved drug epoetin. On June 1, the FDA approved epoetin for the treatment of anemia associated with chronic renal failure. This drug is expensive -- some countries in Europe are paying $9,000 to $11,000 per year per patient for this drug. Since the Medicare program pays the vast majority of expenses for End Stage Renal Disease (ESRD) patients, we held significant discussions with the company that received FDA approval, AMGEN, Inc. Based on those discussions, which included the examination of detailed cost data volunteered by AMGEN, we set a reasonable price to pay kidney dialysis facilities for the administration of this drug in conjunction with dialysis treatment. I should note that the cost data were easy to evaluate because epoetin is AMGEN's first marketable product. The price we announced is $4,650 for each patient receiving epoetin. We must still set coverage guidelines and payment rates outside dialysis facilities, and we plan to evaluate the price in six months. We believe the price we set is reasonable for both dialysis facilities and the taxpayer.

REPORTS TO CONGRESS

The Department has been concerned with the projected cost of the outpatient prescription drug program since discussions of such a benefit began over two years ago. In a May 1989 Report to Congress entitled, "Expenses Incurred by Medicare Beneficiaries for Prescription Drugs", the Department outlined the assumptions used in calculating the estimated $2.8 billion deficit in the drug trust fund. The Department estimates that Medicare beneficiaries who purchased prescriptions in 1988 purchased an average of 21.5 prescriptions in that year. By 1993, outpatient prescription drug users will purchase an average of 23.3 outpatient prescriptions. We also estimate that the cost per outpatient prescription drug will increase from $18.21 in 1988 to $24.26 by 1993.

Perhaps the most difficult element of the program's cost to estimate is that of induced demand. It is commonly acknowledged in the insurance industry that the very act of coverage tends to increase demand for the covered service. This insurance effect is called "induced demand." HCFA actuaries assume an insurance effect which would increase aggregate consumption of drugs by the Medicare population by about 10 percent in 1991, 12 percent in 1992, and 11 percent in 1993.

The Department is also preparing a report to Congress on drug manufacturers' prices and pharmacists' charges as required by the MCCA of 1988. Allow me to briefly describe some of the prescription drug industry trends we mention in our report.

The Producer Price Index (PPI) measures the change over time in the prices received in commercial transactions by manufacturers and producers of various goods. In the case of prescription drugs, the PPI is a measure of the change in prices exacted by drug manufacturers for the prescription drugs they sell. Between 1981 and 1986, the annual growth rate in the PPI for prescription drugs was 10.1 percent. In 1987 and 1988, the PPI increased 9.6 percent and 7.9, respectively.

The Consumer Price Index (CPI) is a widely used measure of inflation in the consumer economy. During the 1970's, the CPI for prescription drugs grew very slowly, much more slowly than the CPI for all items. During the 1980's, however, the CPI for prescription drugs grew very rapidly, far outpacing the growth in the CPI for all items. For example, between 1981 and 1986, the average annual growth rate in the CPI for prescription drugs was 10.2 percent, while the average annual percent change in the CPI for all items was 4.2 percent. This trend moderated slightly in 1987 and 1988, with the CPI for prescription drugs increasing by 8.0 percent and 7.8 percent, respectively, in those years. The CPI for drugs has kept pace with the PPI rather consistently -- essentially, pharmacists have not increased their prices more than what was necessary to keep pace with their increasing costs of purchasing drugs.

In light of the financial difficulty facing the drug trust fund, we are looking with a cautious eye at the very rapid growth in the CPI and PPI for prescription drugs since 1981. We are also aware that, since 1980, the CPI for prescription drugs has risen more rapidly than any other component of the CPI for medical items -- including physician services. Clearly, the drug benefit has the potential to be a volatile program.

I should point out at this time that the implementation schedule for the drug benefit is extremely tight. Implementation on January 1, 1991 will require the timely execution of a number of critical tasks both inside and outside the Department, most important of which is the procurement of the drug bill processors. The full cooperation of all parties will be required in order to accomplish what is, by any measure, a very complex procurement. There is virtually no tolerance in this schedule. Any delay in this process will make implementation within the legislatively required timeframe extremely difficult to achieve.

CONCLUSION

In concluding my statement, I would note that the catastrophic outpatient prescription drug benefit represents a major expansion of the Medicare program, and is laden with enormous administrative challenges. As we forge ahead with implementation, on schedule, we are concerned by the projected underfunding of the drug trust fund and the volatility of prescription drug prices in recent years. We look forward to working with this Committee and others to help ensure that the drug program is financially sound and that it serves Medicare beneficiaries well.

The **Chairman**. Mr. Hays, you started off and ended your statement talking about the underfunding of the Medicare prescription drug program.

Mr. **Hays**. Yes, sir.

The **Chairman**. Wouldn't we have more funds in that program if we got a better deal for the recipients of those programs? For example, like the VA; they get a pretty good deal for those veterans.

Mr. **Hays**. The statutory requirements for drug pricing for the Medicare Program under catastrophic are very specific, and some would argue, quite generous.

The **Chairman**. Generous?

Mr. **Hays**. Generous in the resulting price that Medicare will be required to pay for prescription drugs.

The **Chairman**. Who is the beneficiary of that generosity? Is it the consumer, the taxpayer, the Medicare beneficiary, or the pharmaceutical manufacturers?

Mr. **Hays**. Most directly, the retail drug store which is filling the prescription and is the recipient of the amount that Medicare will pay, along with the co-insurance that the beneficiary will pay. Indirectly, I would assume the pharmaceutical industry in general. But the price that Medicare pays is the price that goes directly to the retail pharmacy that is dispensing the prescription for the beneficiary.

The **Chairman**. You know, I'm on the Finance Committee. I'm wearing two hats today. And I remember the debate on catastrophic—maybe I was absent that day—but it's beyond me how we allowed, or did not put into the catastrophic insurance legislation an incentive or inducement for Medicare to get the best price. How'd we forget that? What happened to us? Where were you? Why didn't you tell us that we were doing wrong? Everyone else has told us what we did wrong.

[Laughter.]

Mr. **Hays**. Well, I was not privy to those discussions.

The **Chairman**. You could have slipped a note under the door.

Mr. **Hays**. Certainly, I believe that those issues were brought to the attention of the various parties who were considering the legislation.

The **Chairman**. You've had some negotiations with the drug manufacturer, Amgen, who's here today. By the way, the only manufacturer who showed up. We're proud of Amgen.

Now, you did some negotiations, I believe, with this company, is that correct?

Mr. **Hays**. We spent the better part of a year in discussions with Amgen over their newly approved, product EPO.

The **Chairman**. Now, I don't know if you negotiated a good price for the Medicare beneficiaries or a bad price. What do you maintain?

Mr. **Hays**. We feel that the price that we have established for the drug is a fair price, both for the Medicare program and for the facilities who will be providing the drug to Medicare patients.

The **Chairman**. Now this is a question that's going to show my ignorance of this field. Why could you negotiate with Amgen on this particular drug and not negotiate on other drugs that we purchase through Medicare?

Mr. Hays. There are a couple of reasons, Mr. Chairman. The pricing mechanism that we have been talking about principally up until this point has to do with the benefit that becomes effective on January 1, 1991, the full outpatient prescription drug benefit. We do not, as you know, today, under Medicare pay for outpatient prescription drugs. The particular drug in question, involving Amgen, is a somewhat unique situation. It is covered under Medicare because of the way in which it is administered in renal dialysis facilities for patients that are receiving kidney dialysis. And we are paying for it as an adjunct to the end-stage renal disease program in a somewhat unique fashion. And it is because we are paying for it through the end-stage renal disease program that we were able to pay for it.

If we had paid for it under the regular Medicare Program following the usual reasonable charge methodology, we would undoubtedly have ended up paying substantially more for this drug.

The **Chairman.** Mr. Hays, I thank you.

Now, Mr. Hays, just one or two more questions. What would you think of the Veterans Administration being appointed? They seem to have gotten a good deal for the veterans. What about the Veterans Administration being appointed to do all the buying for Medicare prescription drugs? What's wrong with that?

Mr. Hays. Well, Mr. Chairman, I think that the threshold question is whether there are so many differences between the Veterans Administration's system and the Medicare Program that they would preclude our taking advantage of the Veterans Administration program. The significant difference, of course, is the fact that the Veterans Administration is in the position of actually providing drugs directly to their beneficiaries, the veterans. It's quite a different situation, I believe, from the Medicare Program where we are dealing with 33 million beneficiaries who will be obtaining their prescriptions through the existing network of 55,000 or 60,000 retail pharmacies around the country. And I guess I would submit that it is one thing for the Veterans Administration, which is in effect a provider of drugs to go through their process, and another thing for the Medicare Program which is primarily a financing mechanism as opposed to a delivery mechanism to do the same.

Be that as it may, I think that it is certainly worth looking at. It may be worthwhile pursuing a demonstration project, or something of that sort. But I would point out that current law does not give us that authority.

The **Chairman.** Well, the law could be changed, if it would be a constructive change. And that's again what the Aging Committee is looking at. But we are going to do something, as I told Mr. Mossinghoff, and I hope he didn't consider this a threat. It was not a threat, it was just a fact that we're going to do something. This institution, this Congress is going to do something. We're going to do something about Catastrophic. I don't know what, but we're going to do something. I wish I knew. And we're going to do something about the escalating costs of drugs. I mean, this institution is going to react to that. And I hope that we don't overreact. I hope we act in the right way.

I'm all supportive of some of the things that the pharmaceutical manufacturers have done. I'm very critical of others. And I've stated those criticisms today.

Mr. HAYS. We certainly wish you well and we would be pleased to cooperate with your staff——

The CHAIRMAN. I'm also believing that we can get a better price, Mr. Hays, for those prescription drugs we are today buying for the Medicare beneficiaries. We can do it. And I thank you very, very much for coming.

Mr. HAYS. Thank you very much, Mr. Chairman.

The CHAIRMAN. Now, I have a final witness this morning. That is George Rathmann, chairman of the board, Amgen Inc., Thousand Oaks, CA.

Mr. Rathmann, you have been a patient man. You have sat here for hours listening to all of this. I don't know if you heard anything new. I heard some things that I certainly didn't know before. During the process of preparing for this hearing, I learned a lot, and I hope that we can put these suggestions to constructive use. We look forward to your statement.

STATEMENT OF GEORGE B. RATHMANN, CHAIRMAN OF THE BOARD, AMGEN INC., THOUSAND OAKS, CA

Mr. RATHMANN. Thank you. The statement that's been submitted also includes a Business Week survey on research and development funding in which Amgen ranks first in terms of dollars spent per employee and as a percent of sales.

The CHAIRMAN. We laud you for being the only manufacturer that we invited who came. You came all the way from California and we are very indebted.

Mr. RATHMANN. Well, I think I can explain that, and it's a credit to the industry as well as us that we're here.

We are the newest biopharmaceutical company. Our first product went on the market, just a month ago. The biopharmaceutical industry only has two companies that presently market products, and we're the second. The industry is very promising; it could continue to expand the pharmaceutical advantage the United States has. As of now, there are only two biopharmaceutical companies based on advanced biotechnology, specifically genetic engineering to make new rationally designed drugs.

Now there are really two reasons why we're here. And one is that we really feel we have a role in helping the public and the Congress to understand this industry. And, as a matter of fact, helping the Pharmaceutical Manufacturers Association, of which we are research affiliates, explain this industry to the Congress and to the public. In a moment I'll explain why. The second reason is that we have held discussions with the Health Care Financing Administration for over a year, and in many respects that's an experience that has not occurred before. There are also some specific reasons for this and we must be careful not to generalize, obviously, and we'll help to share what we know about that relationship with you.

First I'd like to address why we can help in this process. First of all, we have only one product. The investments that have been made in our company are public documents. They're all available. Our sales curves will relate to this one product until our second product is introduced, hopefully some time next year. So that all the information is tied together in a pretty neat package, and can be interpreted from public data. There is no confidentiality issue. The only issue we might have is someone trying to ask us what we're apt to see in sales 2 or 3 years out. That's difficult for us to do, but other than that our information is totally available and there's no reason not to help you interpret that information in the best possible way. And it does give insights into the nature of the process of creating a new pharmaceutical drug.

By the way, ours is a 1-A drug, a drug of significant therapeutic value. Our next one will probably also be the same. It's one of those drugs that represents a new molecular entity of great important therapeutic gain, recognized by the FDA.

The CHAIRMAN. Now, how many of those drugs came on the market last year?

Mr. RATHMANN. On the average each year there are between two and three of such drugs.

The CHAIRMAN. Of course, this is a very, very important breakthrough, is this correct?

Mr. RATHMANN. We're careful about that word, but yes, it is.

The CHAIRMAN. You hope that it is, all right?

Mr. RATHMANN. OK.

Now, if we turn to the discussions that we had with the Health Care Financing Administration, we elected over a year ago to have those discussions because we felt there was a lot of information we needed, and were prepared to share. But there was also a very special circumstance because of the end-stage renal disease program. This particular drug, which will eliminate 300,000 transfusions per year, is tied primarily to that end-stage renal disease population.

As a result of that, it was clear that there had to be some understanding of the price tag for this drug. So we provided the background information I just disclosed about investments, what the cost of those investments were, how long they'd been going on, that our company has been in business for 9 years, and this is our first product. So the investment is extreme. In fact, for that drug, if we allocate a portion of our investment, even a reasonable portion, it comes out to be substantially higher than the $100 million that has been used here today. But it is a breakthrough drug.

Now, there are a number of questions that have been raised about what kinds of discussions we had with the Health Care Financing Administration. It was truly discussion. We presented a lot of information. They told us some of their concerns, some of their ways of measuring. They requested a lot of additional information; about what cost savings would be associated with Eposen. What would be the benefits to the quality of care in this country. We did a thorough analysis over that year and provided them with the information done both by our own surveys, and other firms. So they had a measure of just how valuable this product was going to be. They had an opportunity to see tapes of people that were on the drug, physicians, leading world figures who could acknowledge the importance of this drug, as well as looking at the cost effectiveness data. And the Medicare people also felt that all cost information was important, even if it didn't directly impact the Medicare budget itself. And that was quite helpful.

The **CHAIRMAN**. Could I ask you a question?

Mr. **RATHMANN**. Sure, go right ahead.

The **CHAIRMAN**. You negotiated with HCFA and you found those to be constructive, I guess.

Mr. **RATHMANN**. Yes, we——

The **CHAIRMAN**. Ultimately——

Mr. **RATHMANN**. We avoided the word, negotiation. We felt that it was more appropriate to have information exchanged.

The **CHAIRMAN**. All right.

Have you ever had any discussions with the Veterans Administration?

Mr. **RATHMANN**. In answer—if you'd let me pose the question a little differently. How will our product be priced? It will have one price. We don't have any plan for the foreseeable future to have a differential pricing strategy. Now, it may be brought about by a competitive situation, and then we have to address that. But at the present time we have one price and that's the price. And that's why I say there wasn't exactly negotiation. We elected to establish our price before HCFA established their reimbursal. But we had a measure of how they were going to evaluate the cost effectiveness of this drug.

The **CHAIRMAN**. I know absolutely nothing about all this, and I would admit it. But I would like to ask you a question because you've been in this community for awhile, and hopefully this drug is going to be a success and improve the quality of life of hopefully thousands, millions of Americans, or people worldwide.

Were you surprised at any of the charts that you've seen today, for example about the variation of international prices, or this one showing when the patent expires on a brand name it keeps going up even after the generics have hit the market? Did any of this surprise you, or is this something that's pretty well known everywhere?

Mr. **RATHMANN**. The information that's least well known to our company is really with respect to the pharmacists. We have not been that acquainted with that part of the market. A lot of the other information has been examined by people in the company and we are aware of it. As a matter of fact—and some of these points were revealed to us in these discussions with HCFA. That was a great educational period. One of the issues that came up was international pricing. We provided all the data available and, in fact, the domestic pricing differential with the international price is much more favorable to the United States, in our case, than it is on those charts.

The **CHAIRMAN**. I sort of took on the pharmaceutical manufacturers' Mr. Mossinghoff a little bit, because of the so-called tax breaks. I voted for all those. So I can't charge those against him.

Mr. **RATHMANN**. Would you like to know our number?

The **CHAIRMAN**. I voted for all those because I thought it would help in finding cures for some of the major diseases, illnesses that we have. And I have no apologies about it. I don't like, though, people saying, or not giving the taxpayer, or the tax code any credit for what we intended for them to do in the beginning. And that's where I have a little difference with my friend, Mr. Mossinghoff.

But I bet with you, now I'm not being critical, it's not critical, but with you, you probably helped develop this drug because of the tax breaks, or the subsidies?

Mr. RATHMANN. I hate to disappoint you. In fact, we have not received any tax benefit from the R&D credit. Remember, we're losing money right up to right now, or just about breaking even. Tax benefits help the people that make money. They don't help that much until a company gets into a profitable position. I think we have a credit of about $3.8 million that someday we'll be able to use as our profits reach that point. So the tax implications were not a factor in our thinking. And unfortunately, we're not an exception here. We are an exception in some cases. We have to watch that. But in the case of tax credits they're not as helpful to a startup company. Remember, we started 9 years ago, and we have no significant profits during that entire time.

The CHAIRMAN. They're more helpful to the established companies?

Mr. RATHMANN. Well, let's not be negative. I think it's an encouragement to an established company to invest in R&D and grow their R&D. So it's a positive incentive for a good thing. It just doesn't happen to help with startup.

The CHAIRMAN. Did you have any other comments there, Mr. Rathmann?

Mr. RATHMANN. I was going to address some of the questions that had come up, and that was all.

For example, a question that was raised, why don't normal market forces operate? I think one of the things that has to be kept in mind besides all the other factors that were raised in that discussion, is with a product like Epogen, the breakthrough products, if you want to call them that, there is no alternative therapy. There is a crushing need for this product, and there's no way of measuring cost or price directly by saying I'm going to substitute this product for another product. It's very difficult to make a pricing decision when the only alternative therapy is a much less satisfactory transfusion of blood at a very high level. And, in fact, even transfusions don't restore the patient to the same state of health.

Another question that came up, I thought I'd comment on, was foreign competition. In contrast to the picture you saw, where a very, very small penetration is from foreign companies, the biotechnology industry in this country is threatened by very severe foreign competition. And the reason for that is the maturation of our competitors overseas, and this is a new industry. New things give an opportunity for changing market shares, and foreign competition could very drastically change its market share in this country, and is targeting to do so. And as of now, foreign competition lurks just beyond our borders. Very, very shortly we could have competition for this product, because it has been difficult for us to assert our patent position. And that's a serious problem. And that ties into patents as well.

[The prepared statement of Mr. Rathmann follows:]

AMGEN

STATEMENT BEFORE

THE SENATE SPECIAL COMMITTEE ON AGING

Presented By

George B. Rathmann
Chairman of the Board
Amgen Inc.

Mr. Chairman and Members of the Committee:

I am George Rathmann, Chairman of the Board of Amgen Inc., a biotechnology company located in Thousand Oaks, California. I am here today to share with you the very limited experience in drug pricing of perhaps the newest research-intensive manufacturer of prescription drugs. Amgen has one FDA-approved product which it has been marketing for only about six weeks.

Since its founding in 1980, Amgen has been dedicated to the development of human pharmaceuticals using advances in recombinant DNA technology and molecular biology. On June 1, 1989, Amgen was granted a license by the Food and Drug Administration to manufacture and market its first pharmaceutical product, EPOGEN® (Epoetin alfa), recombinant human erythropoietin. On June 2, we began shipping EPOGEN®.

In healthy adults, erythropoietin is produced in the kidney in response to changes in oxygen availability in the bloodstream. Erythropoietin travels to the bone marrow, where it stimulates cells in the marrow to mature into red blood cells which are released into the bloodstream. Red blood cells carry oxygen to, and carbon dioxide from, tissues and organs throughout the body.

Since the kidney is the principal site of erythropoietin production in adults, renal insufficiency almost always results in anemia, or a shortage of oxygen-carrying red blood cells. Of the 108,000 Americans receiving maintenance dialysis, more than 75% are anemic and an estimated 25% are so severely anemic that they require blood transfusions to survive.

First cloned and developed by Amgen scientists, EPOGEN® has the same amino acid sequence and biological effects as natural erythropoietin. The first clinical trials of EPOGEN® were begun by Amgen in 1985. In the multicenter clinical trials that followed, EPOGEN® proved effective in correcting anemia in over 95% of the patients treated, and it virtually eliminated the need for blood transfusions. EPOGEN® therapy significantly increased patients' quality of life, including their energy and activity levels and capacity to exercise. It enabled some patients to return to work. The product was generally well-tolerated without serious adverse effects.

Through the end-stage renal disease program, Medicare covers most of the costs of health care provided to patients on dialysis. Medicare therefore will be the principal payer for EPOGEN® for patients on dialysis. While payment for EPOGEN® will have an impact on the Medicare budget, this budget will realize significant offsetting economic benefits. In particular, the cost of blood transfusions and androgenic steroids, and the side effects and risks of these therapies (including AIDS and hepatitis), should be virtually eliminated, with significant savings to the Medicare program.

In addition, the number of successful kidney transplants should increase. Patients who receive transfusions are at risk of developing antibodies which increase the incidence of kidney transplant rejection. Patients who will never have to receive a transfusion, because of EPOGEN®, will not develop these antibodies. Therefore, we expect that more patients will be eligible for transplantation. Furthermore, preliminary reports indicate that the antibody levels of previously transfused patients may decline over time as they no longer receive transfusions.

Additional areas of savings to the government are more difficult to quantify at this time, but early evidence suggests that, if their anemia is prevented, fewer patients will become unemployed when they begin dialysis. As many as 25% of patients on dialysis report that they cannot work because of fatigue, tiredness and lack of energy -- all of which are symptoms of anemia, which EPOGEN® corrects. At one center participating in the Amgen clinical trials, 16% of patients were reported to have returned to work after EPOGEN® therapy corrected their anemia. When a patient works, not only does the government collect increased tax revenue, but in many cases, disability payments are eliminated.

In 1985, Amgen licensed U.S. EPOGEN® marketing rights to all indications except dialysis to Ortho Pharmaceuticals, a subsidiary of Johnson & Johnson. The status of Ortho's U.S. marketing rights, if any, is the subject of a current arbitration proceeding. Rights to market EPOGEN® in foreign countries have also been licensed to other companies.

Recognizing that approximately 90% of the patients in Amgen's retained market (i.e., patients with end-stage renal disease on dialysis) are Medicare beneficiaries, Amgen approached the Health Care Financing Administration (HCFA) in June 1988, to discuss coverage and reimbursement issues. Over the course of the last year, Amgen and HCFA met frequently, reviewed available data, and prepared numerous analyses of the clinical benefits and potential economic impact of EPOGEN® therapy.

On June 22, 1989, HCFA announced that, for at least the next six months, Medicare will pay dialysis facilities an additional $40 per dialysis session when EPOGEN® is administered. Prior to that announcement, in conjuction with FDA's approval of EPOGEN®, Amgen announced its price, $10 per 1,000 units. (In our clinical trials, most patients received between 2,000 and 8,000 units, three times per week, depending on the patient's weight and other factors.)

Amgen understands the Committee's interest in drug pricing issues. In pricing EPOGEN®, Amgen considered its historical investment in EPOGEN® research and development (including the cost of capital to fund those efforts), its expected future expenditures, and the special characteristics of the dialysis marketplace. The price Amgen set is well below the current average worldwide price for erythropoietin, which is approximately $14 per 1,000 units.

Reports in the media have suggested that Amgen intends to reap unreasonable profits from the sale of EPOGEN®, at the expense of the American taxpayer. In particular, one source has alleged that it costs Amgen $140 to manufacture a patient-year's supply of the drug, with the further inference that this is Amgen's total cost. This is grossly inaccurate.

It is important to understand that the costs of bringing EPOGEN® to patients include not only the costs of bulk manufacturing, but also the costs of other manufacturing steps, vialing, packaging, product liability insurance, distribution, continuing research and development to improve the product, and perhaps most importantly, the enormous investment necessary to discover EPOGEN®, test it, and bring it to market. In addition, because EPOGEN® is a completely new therapeutic entity, Amgen must provide extensive medical education and medical information support for the product in order that physicians, nurses, and other health care professionals are properly informed about its use.

The cost of bringing EPOGEN® to market must also include the cost of the corporate infrastructure required to support the effort. Such costs include human resources, accounting, sales and marketing, and administration functions, as well as general overhead costs. Furthermore, Amgen estimates that next year its combined federal and state tax rate will be approximately 40%.

I would like to emphasize the need to include in the price of a new drug product a reasonable return to the manufacturers' investors. Over the course of its eight-year operating history, Amgen has spent approximately $338 million, primarily on research and development, including capital improvements. In fact, according to a Business Week survey of companies in the United States, Amgen ranks first in R&D dollars spent as a percent of sales (89.5%), as well as in R&D dollars spent per employee ($112,269). Business Week reported that Amgen invested more in research and development than any of its competitors: 729% more in 1988, and an average of 448% more over the past five years. Mr. Chairman, I would like the article from this special issue on "Innovation in America" to be included in the record as part of my testimony.

This significant investment in R&D has led to the development of two of the most promising biotechnology products, EPOGEN® and NEUPOGEN™. (NEUPOGEN™, recombinant granulocyte-colony stimulating factor, is in Phase III clinical trials. NEUPOGEN™ stimulates the production of the white blood cells that fight bacterial infections, and appears promising in its application to patients with extremely low white blood cell counts brought on by chemotherapy.)

Typically, in the hopes of identifying the handful of products that will be therapeutically valuable, a company must proceed with research and development for many products, only a few of which become commercially successful. Furthermore, it is necessary to incur the costs of developing basic technology which is essential to the development of therapeutic products. Therefore, the cost to develop a product such as EPOGEN® necessarily includes the cost of basic technology as well as the cost of R&D on products which have not proven to be successful. The true cost of developing EPOGEN® has been more than half of the company's total expenditure of $338 million.

Approximately $185 million of the money to fund these extraordinary research and development efforts has been in the form of equity capital, much of which was invested at significant risk by investors who believed in the quality of the company's science and its management. Today the United States enjoys a clear lead in biotechnology. We are ahead of Europe and Japan in the research and development of new products from biotechnology. We have achieved this lead through the support of private capital. Unlike our foreign competitors, many of whom are supported by direct government subsidy, the U.S. biotechnology industry has been financed almost exclusively by private capital. We are proud of our progress and ask for no subsidy from the government in any form. At the same time, in order to maintain our industry's lead, it is imperative that those who have invested in our industry be able to achieve a return on that investment.

Unless Amgen achieves from EPOGEN® an adequate rate of return on these investments, it is unclear that Amgen, or other innovative biotechnology companies, will be able to access the capital markets to fund biotechnology research and development in the future. Without an adequate rate of return, investors will not continue to invest in this promising but risky area of new technology. I want to emphasize that, at this time in the history of biotechnology, investor anxiety is extremely high. Amgen's success or failure with EPOGEN® will be extraordinarily important in investor thinking.

Some of the risks associated with investing in biotechnology companies have to do with significant delays in achieving appropriate patent protection, with the potential loss to foreign countries of much of the intellectual property developed by our industry. We expect, for example, that EPOGEN® might have to compete very soon with a Japanese-made product, despite our assertions in court and before the International Trade Commission that the Japanese company is violating our patent.

As I mentioned earlier, EPOGEN® is Amgen's only human pharmaceutical approved for sale. Apart from a small line of biologicals for the basic science research market, the company has no other products to sustain it as it continues efforts to develop other "breakthrough" products. At the same time, since EPOGEN® is Amgen's only product, the degree of profitability from EPOGEN® will be readily apparent to Medicare, to the Congress, to all observers, from the company's audited financial statements filed periodically with the Securities and Exchange Commission.

Taking into account these factors, Amgen has made every effort to balance its responsibilities to patients and society with its responsibilities to employees and stockholders in pricing its first product. We believe that we are selling EPOGEN® at a reasonable price, 30% below the price set by our licensee abroad.

In summary, the experience of Amgen in pricing its first pharmaceutical product has been uniquely affected by characteristics of the company and of its retained market. Of paramount importance in establishing a price for this product has been the company's need to survive. Returning reasonable value to its investors is an essential element of that survival.

Amgen also has taken seriously its obligation to insure that patients who need EPOGEN® will receive it as soon as possible. Discussions with HCFA centered on that goal, and on the government's obligation to conserve Medicare trust funds. HCFA, like the FDA, gave recombinant erythropoietin high priority and acted rapidly and responsibly in making it possible for patients to receive this valuable therapeutic.

Amgen would have preferred a reimbursement methodology which created more incentives to provide adequate amounts of EPOGEN® to anemic patients, but we are pleased with the relationships we have developed at HCFA. We are hopeful that information gathered over the next six months will suggest ways to fine tune the methodology as required to improve patient access.

I appreciate the opportunity to discuss these important issues with this Committee. I would be happy to answer any questions you may have.

The Chairman. Mr. Rathmann, your Senator, Senator Wilson, is very sorry he could not be here with his constituent this afternoon. He wanted me to ask you this question.

Given your company's experience in discussing reimbursement levels for its drug, Epogen, with the Health Care Financing Administration, do you expect to have similar discussions in the future with respect to other products now in your research and development pipeline? Is this going to happen in the future?

Mr. Rathmann. Well, I suspect that we will have similar discussions on occasion. But certainly, this is a unique product for which this was really called for as a very important and necessary thing to anticipate. Where the Medicare participation would be a much less significant portion of how the drug would be financed, we probably wouldn't do it. And as I understand it, if they were obligated to have as extensive discussion for every product that's introduced, I think they'd probably have to be staffed many, many times greater than they are. So, I suspect it's not practical. I think it should be examined for every one, but I wouldn't want to say that we would do it every time.

The Chairman. Also, Senator Wilson wanted you to state in the record some of the important therapeutics developed by biotechnology and what they have been to date, and I don't know if you want to do that now.

Mr. Rathmann. I can send you that information on other biotech drugs. There have been half a dozen, and they're all very important. This is probably one of the most important.

[Subsequent to the hearing, the following information was received for the record:]

Mr. Chairman, to date the American biotechnology industry has introduced nine products. These products have all made positive contributions to the healthcare of people not only in the U.S. but around the world. Those products, their introduction date, and their uses are as follows: *Humulin*, October 28, 1982, injectible insulin; *Protropin*, October 12, 1985, hypopituitary dwarfism; *Intron A and Roferon A*, June 4, 1986 hairy cell leukemia, *Orthoclone OKT3*, June 19, 1986, allograft rejection, *Recombivax HB*, July 23, 1986, hepatitis B vaccine, *Humatrope*, March 8, 1987 hypopituitary dwarfism, *Activase*, November 13, 1987, thrombolysis, and *EPOGEN®*, June 1, 1989, chronic renal failure.

The Chairman. Well, finally, I'll end this hearing, almost as I started off by asking one of our first witnesses, what's the role of the Government in all of this? Some people say hands off, free enterprise, let the market place decide. What should we do? What do you think this committee should do? We're trying to be responsive to the elderly population and to all the population of the country. What should we do in this committee, what should we do in the Congress and the Government about some of these issues we've discussed?

Mr. Rathmann. Well, obviously, you're attempting to understand, and that's the first step. And I think we all should work with you to help you understand as much as we know. And none of us understand it all. It's a matter of helping each other.

I think we all recognize that the burden of the health care of our population is a very significant part of our gross national product and the Government is a very significant player. I think it is important, however, not to ignore quality. And one of the most difficult issues is to factor in correctly the quality requirement along with some other easier measurement which is cost. I sense that from this group—

The **Chairman**. By the way, Senator Warner kept emphasizing quality this morning. I'd like to emphasize quality, and I certainly agree with you.

Mr. **Rathmann**. Well, we're with you. If you can help, we will.

The **Chairman**. Well, we just don't know quite where to go now, but I'll tell you we're going somewhere, and before long we're going to have another hearing. I hope that you can talk to some of your colleagues who are in the pharmaceutical business, some of the manufacturers to convince them that we don't have horns, that we're looking for answers, that we hope that they will participate with us in some of these future discussions.

Mr. Rathmann, we thank you very much and we thank all of you very, very much today as our witnesses.

This committee is adjourned.

[Whereupon, at 1:21 p.m., the committee was adjourned, to reconvene at the call of the Chair.]

SKYROCKETING PRESCRIPTION DRUG PRICES: TURNING A BAD DEAL INTO A FAIR DEAL

THURSDAY, NOVEMBER 16, 1989

U.S. Senate,
Special Committee on Aging,
Washington, DC.

The committee met, pursuant to notice, at 9:30 a.m., in room 628, Dirksen Senate Office Building, Hon. David Pryor (chairman of the committee) presiding.

Present: Senators Pryor, Heinz, Bradley, Cohen, Pressler, Wilson, Reid, Warner, and Kohl.

Staff present: Portia Porter Mittelman, staff director; Christopher C. Jennings, deputy staff director; Jeffrey R. Lewis, minority staff director; David Schulke, chief of oversight; Jennifer McCarthy, professional staff; and Thorne Sparkman, research associate.

OPENING STATEMENT BY SENATOR DAVID PRYOR

The Chairman. Good morning, ladies and gentlemen. We are assembled here today to continue this committee's examination of the prescription drug crisis which began with our first hearing on July 18 of this year.

There is no question that we face a growing crisis in the United States due to rising prescription drug prices. We are about to strike the new Medicare drug benefit from the catastrophic health insurance legislation because of rising drug costs. We are doing this at the very time when drug costs represent the highest out-of-pocket health care cost for three out of every four Americans.

It is not just elder Americans who are suffering. State Medicaid programs that serve the poorest Americans have struggled through this decade by chopping and chiseling at their drug coverage. The States have raised copayments, cut benefits, imposed coverage restrictions, held down pharmacy reimbursements—in fact, they have done everything but get the drug manufacturers to stop raising their prices at a rate which is three times faster than inflation.

Medicaid drug spending is now over $3.3 billion a year, even more than we spend on doctors in that program. I am going to insert a letter for the record from California State Assemblymen Philip Isenberg and William Baker on what the State of California has attempted to do to respond to the spiraling cost of drugs in their Medicaid program.

[The letter follows:]

Phillip Isenberg ASSEMBLYMAN, TENTH DISTRICT
CALIFORNIA LEGISLATURE, STATE CAPITOL, SACRAMENTO, CA 95814 (916) 445-1611

CHAIRMAN, ASSEMBLY JUDICIARY

COMMITTEES:
ELECTIONS, REAPPORTIONMENT & CONSTITUTIONAL AMENDMENTS
HEALTH
JUDICIARY
REVENUE & TAXATION
WATER, PARKS & WILDLIFE

November 14, 1989

Senator David Pryor, Chairman
U.S. Senate Special Committee on Aging
Room G31, Dirksen Building
Washington, D.C. 20510

Dear Senator Pryor:

We are pleased indeed that your committee is holding a special hearing on the price of drugs purchased by state Medicaid programs.

We believe that the federal government and the various states can save millions of dollars every year by negotiating the price of drugs purchased for indigent health care, and we are trying to do just that in California.

California's Medi-Cal program buys $134 million annually worth of drugs on its formulary that are made by only one pharmaceutical manufactor. Medi-Cal pays list price for 222 such "single source" drugs. It receives no discount or rebate.

But most other major health programs, such as the Veteran's Administration, negotiate prices 20 to 80 percent less than Medi-Cal pays for the same products.

Some examples:

DRUG	USE	LOWEST PRICE	MEDI-CAL PRICE
Lo-Overal	Birth control pill	$ 1.75	$14.53
Tolectin	Anti-arthritic	9.30	37.68
Lopressor	Heart drug	11.90	36.40
Naprosyn	Anti-arthritic	34.00	73.56
Tagament	Anti-ulcer	27.60	54.90
Trandate	Heart drug	20.50	37.34

We estimate that the federal government and the state of California could save at least $40 million if the price was negotiated in return for being listed on the state's formulary.

There is a substantial financial benefit to drug companies when one of their products is listed on the formulary. It means that doctors may prescribe these drugs without prior approval. Sales of the drug increase dramatically through Medi-Cal use, and physicians who become familiar with the drug through Medi-Cal prescriptions tend to prescribe the same drug to their private-pay patients.

Assemblyman Bill Baker (R-Danville) introduced Assembly Bill 2148 earlier this year to authorize the California Department of Health Services to negotiate rebates from manufacturers of single source drugs.

Under AB 2148, such drugs could not remain on the formulary unless the manufacturer agreed to pay a rebate within a 90-day negotiation period. Among the factors to be considered by the state's rebate negotiators was the price paid by other large volume purchasers. They also would have been required to consider the health needs of Medi-Cal beneficiaries.

Incredibly, the drug manufacturers' main argument against AB 2148 went like this:

One, they said, such a precedent in California could spread to other state Medicaid programs, Medicare and other insurance-type health programs. Two, widespread use of such rebates would have a major impact on drug pricing.

Therefore, the drug manufacturers said, they would not agree to pay rebates in order to keep a drug on the Medi-Cal formulary.

The manufacturers also said there would be conflicts with state and federal anti-trust laws if AB 2148 was enacted.

AB 2148 failed in its first committee. Under heavy pressure from the drug companies, it mustered only 4 votes.

Later, Assemblyman Phil Isenberg (D-Sacramento) and Baker put a provision into an unrelated bill that would allow the Department of Health Services to use emergency regulations to pull a drug off the formulary, effectively giving the department the hammer it needs to negotiate drug rebates. It remains to be seen if the department can use this authority.

Certainly, we urge the department to use this power to negotiate single source drug prices.

We believe the drug manufacturers' argument that California can lead the nation into dramatic taxpayer savings on publicly purchased pharmaceuticals.

Thank you for offering us this opportunity to comment for the record.

Sincerely,

Phil Isenberg
ASSEMBLYMAN PHIL ISENBERG

William P. Baker
ASSEMBLYMAN BILL BAKER

The CHAIRMAN. I would like to quote from the letter, which is dated November 14, 1989. "We believe that the Federal Government and the various States can save millions of dollars every year by negotiating the price of drugs purchased for indigent health care, and we are trying to do that in the State of California."

The letter goes on to describe the negotiating process, involving the use of leverage due to the tremendous amount of drugs being purchased by the State's Medicaid program.

I would also like to read two other sentences from this letter: "Incredibly, the drug manufacturers' leading argument against Bill No. 2148 went like this: 'One,' said the drug manufacturers, 'such a precedent in California could spread to other State Medicaid programs, Medicare and insurance type programs. Two, the use of widespread rebates would have a major impact on drug pricing.' "

The legislation, I might say, was defeated. But, that is nevertheless exactly what we are attempting to do, to have a major impact on drug pricing, ultimately for the sake of the consumer, the States, and the Federal Government. That is what this hearing is about.

The escalation of prices of prescription drugs is not over. In fact, it may be just beginning. Drug prices are now rising faster than almost any type of Medicaid spending, and Medicaid, with just one exception, is the fastest growing program in State budgets. But it is not just the poorest Americans who are suffering, and it is not just a problem for Government programs. It is a problem for people. It is a problem for people who have saved. It is a problem for people who have planned for their retirement years. We will hear from some of those this morning.

Because of skyrocketing drug prices, ordinary citizens are going to extraordinary lengths to find less expensive drug treatment. Sometimes, they must spend their life savings for prescription drugs. People with AIDS in our country are now being pushed into buying their life-sustaining drugs from foreign countries. Now one of the companies that made the price of its drug so high is asking the U.S. Government Customs Service to seize these low-cost drugs at the border, so they can continue in their price escalation and profit increases.

Why should anyone in America have to risk arrest to find a reasonably priced prescription drug to save their life? It is our responsibility to find a way to get drug costs down to a reasonable level. We should look at what other governments are doing abroad to keep drug costs low.

We will be doing just that today. We also will look to see what the smartest people in the private sector in America are doing to lower drug prices.

Our witnesses today are going to help us find some solutions to this crisis of affordability of prescription drugs.

First, however, I would like to address the drug companies, the pharmaceutical manufacturers' latest attempt to muddy the waters on this issue. Yesterday, each member of this Committee received from the Pharmaceutical Manufacturers Association a letter stating a purported attempt to rebut the Committee's majority staff report that was released at our last hearing.

I would like to say that I stand by that report. I think it is interesting to note that the drug manufacturers failed to mention in their latest information to the Committee that they spent almost half of their research and development budget on "me-too" drugs.

Here's what a former drug company executive, then an investment analyst on Wall Street, told the Washington Post only last year: "A typical drug firm currently spends 15 to 20 percent of its research dollars on high-risk investigation of breakthrough products, 30 percent on developing improved versions on existing drugs, and the balance, somewhere between 50 and 55 percent, on so-called 'me-too' drugs, proprietary versions of drugs that are on the market and that have been successful."

I might add that these are high-profit items.

Recently another former drug company executive had his speech appear in a publication, entitled Vital Speeches of the Day. In that speech, this former executive said "Senator Kefauver was worried about administered prices. These are administered markets. There is nothing efficient about them. This is the reason so much of the R&D in industry is directed at increasing profits, not discovering products. In some market segments, most of the research is aimed at getting or keeping a piece of a large, profitable market without offering any new therapeutic advantage. Regulators have been outfoxed and out-financed."

I could go on and on this morning with further revelations, but I believe everyone knows what the prescription drug industry cannot afford to admit. We can and we should and we must use our leverage to bargain over the price of "me-too" drugs. I look forward to today's witnesses, who will tell us how to do it, and how to do it right.

Ladies and gentlemen, also let me announce, if I might, that we are going to have an interesting follow-on meeting on this issue at 1:30 this afternoon in this room. We are going to set up a big table here, and any and all participants here today—witnesses, Senators, staffs, panelists, drug company representatives, the press—and anyone who desires to come are going to have a round table discussion on where we are and what we need to do.

It will be off the record. We hope that it will be informal to the extent that we can all let our hair down. We have never tried anything like this before, but once again, we extend an invitation to all of you to join us, to listen, to add your two cents worth, and to participate. Especially the drug companies, who I cannot get to testify, in a formal setting, possibly might come and answer some of the questions about why drug prices are escalating at the rate they are today.

That will be at 1:30 in this room.

We have our vice chairman with us here, Senator Heinz.

STATEMENT OF SENATOR JOHN HEINZ

Senator Heinz. Thank you very much, Mr. Chairman. I commend you for not only holding this important hearing, but two very timely and critical hearings in a row. The one yesterday was on a different kind of drug problem, illegal drugs, and this one of course deals with legal and literally life-saving drugs.

The CHAIRMAN. Well, let me interject. The hearing yesterday was on illegal drugs, today's it is on immoral prices of prescription drugs. Senator Heinz, I hated to interrupt.

Senator HEINZ. But you couldn't resist.

The CHAIRMAN. I could not resist.

Senator HEINZ. And those drugs are of critical importance to 31 million—in this case, certainly law-abiding—elderly Americans. I think it is important to recognize that as we meet here, Congress is on the threshold of repealing the first prescription drug benefit ever enacted, the benefit that is part of the catastrophic coverage that we enacted last year.

Clearly we are rolling backward in this area, rather than forward. While Congress may feel snakebitten with catastrophic coverage overall, I think in terms of prescription drug benefits, that feeling is only temporary. I think out of this hearing, as Senator Pryor has suggested, we can develop some promising initiatives and measures that will hold down drug costs while assuring that there is access to safe prescription drug use, when needed.

Most Americans are aware of the chronic conditions, including hypertension, arthritis, cardiovascular diseases, that are the constant companions of aging, and require the constant regulation of prescription medications.

The elderly who depend on those drugs to relieve painful or unpleasant symptoms, to improve the quality of their lives and maintain their independence, may take up to 14 different prescriptions during the course of a year to treat one or more conditions. Unfortunately, over half of those who use prescription drugs regularly have no insurance coverage for that type of expense, and they are very vulnerable to skyrocketing costs.

As we learned in the process of drafting the prescription drug benefit for the catastrophic coverage bill, three out of four seniors reported that their out-of-pocket expenses for drugs took by far the biggest bite out of their health care pocketbook. Many are forced to factor those costs into their family budgets, where they compete with dollars needed for food, clothing, and heating costs.

In the end, people literally often decide they are going to go without the medication they need, because they simply can't afford it.

One of my constituents, from Selinsgrove, PA, recently wrote to me that she takes four prescription medications daily, and each has increased in price by 10 percent or more in recent months.

For a family on a limited income, 10 percent more for a drug bill that could be running $125 or maybe more a month, means cutting 10 percent from what is left after paying rent and taxes, which means taking 10 percent off food and clothing budget, or worse, not taking the medication.

I think this hearing is timely; I almost want to make a plea to our colleagues. As we go through the process of dismembering the Catastrophic Coverage Act, which is flawed in many respects, and does need a substantial revision, that we pull from the ashes of that program one very important element: the drug review screen.

The advantages of the drug utilization review element are well known. They include access to a comprehensive record of a patient's treatment program and built-in alerts to notify a pharmacist of allergies or potential adverse drug interactions. We know that is possible since some drug chains offer such a service now.

The Inspector General recently estimated that a drug utilization system could save $4.5 billion a year in avoidable hospital costs as well as thousands of lives, just by keeping seniors from being overmedicated, or inappropriately medicated. That's the particular kind of cost savings I want to talk about.

Mr. Chairman, again I congratulate you on this hearing. I look forward to the testimony of our witnesses here today.

The **CHAIRMAN**. Thank you, Senator Heinz.

Senator Reid.

STATEMENT OF SENATOR HARRY REID

Senator **REID**. Thank you very much, Mr. Chairman, for providing members of this committee with an opportunity to further examine the current crisis of prescription drug costs.

I would also like to take this opportunity to thank the group of witnesses who are lending their valuable time and testimony to us here today.

It seems likely that the prescription drug coverage in the Medicare Catastrophic Act will not go into effect, as Senator Heinz has explained. The need to stop rising drug costs, therefore is all the more urgent. The first panel of witnesses will offer testimony that is all too familiar to me.

I receive many, many letters recounting the horror of steep and steady drug price increases, price increases that force people to go without a week's worth of necessary medicine, or without meals at the end of the month.

Mr. Chairman, I would like to share a bit of one of these letters with you and the other members of this committee. This letter is addressed to me.

> Dear Senator, I am 86 and my wife is 80. Both "headed south," of course—older. We have been relatively fortunate so far, but worry every day about going absolutely broke, should luck forsake us for long. Our biggest expense now, surprisingly to us, is prescription drugs. We challenge them every one, and take turns skipping or refusing to use one or so at a time. Some luck. Doctors are prone, as we know, to dish out the pills. We fight it.
>
> But in 1988, our drug bill ran close to $2,000. The prices boggle our minds. Maybe that needs looking into, also. We work all the angles, we are members and users of AARP, etc. It is still frightening.

I won't read the rest of the letter, from this individual from Boulder City, NV. I think it speaks volumes for why we are here today. I am hopeful that perhaps some of the negotiations that my friends from Boulder City have been doing with their own budget, drug purchases and physicians can be done by those who sell them drugs.

Those testifying here today have had various experiences in bargaining for lower drug prices. I trust we will learn something from those successes and failures and move closer to bringing down the cost of prescription drugs.

Again, Mr. Chairman, thank you for holding this hearing.

The **CHAIRMAN**. Senator Reid, thank you.

Senator Cohen.

STATEMENT OF SENATOR WILLIAM COHEN

Senator COHEN. Mr. Chairman, I do have an opening statement which I would like your permission to submit for the record.

I would say that all of us, along with Senator Reid, have received poignant letters from powerless people. That is why this hearing is so particularly important, to see if we can at least explore what alternatives may be available.

I also want to commend the staff. That study that was done was truly staggering, in terms of its revelations. I am not sure whether it amounts to price fixing on the part of some, but it comes close to it, in my judgment.

So I will reserve my comments until we hear from the witnesses.

[The prepared statement of Senator Cohen follows:]

OPENING STATEMENT OF SENATOR WILLIAM S. COHEN

SPECIAL COMMITTEE ON AGING

November 15, 1989

Mr. Chairman, I commend you for convening this hearing. It is clear that you are determined to be thorough in your Committee's work on issues relating to prescription drugs. The hearing on prescription drugs that the Aging Committee held earlier this year was very successful in raising issues of concern to the nation's consumers -- especially elderly consumers since it is they who are most in need of and dependent on prescription drugs. I am sure that this hearing will yield comparable progress toward getting the nation's taxpayers more for their tax dollars spent on prescription drugs.

As the recent analysis by the staff of this committee points out, the cost of prescription drugs is the fastest growing component of state spending on Medicaid, which is itself one of the most rapidly rising components of state budgets. During its previous fiscal year, Maine's Medicaid program spent $26.7 million for prescription drugs. State officials estimate that this year the program will spend more than $30 million. Rising prescription drug expenditures has prompted Maine to plan the establishment of a formulary commission for the purpose of devising a system for controlling these costs. I am certain, therefore, that concerned parties in my state will be very interested in the findings of this Committee.

Mr. Chairman, again, I commend you on holding this hearing and for your efforts to shed light on the important issues relevant to prescription drugs.

The **Chairman**. Thank you, Senator Cohen.

Not all of the people in our country who are affected by the high prices of prescription drugs are what you would call poor. Some of those individuals are those who have planned, saved, worked hard for their retirement years. Also, there are those who depend specifically on unique drugs that cost a tremendous amount of money. These drugs continue in their price escalation.

We are going to hear from two witnesses today who I think fit well into that category. The first is Mr. Jake Green, from Winchester, KY. Mrs. Leona Bivens, from Seal Beach, CA, is our second witness. Our third witness on this panel is Mr. Derek Hodel who is the executive director of the People with AIDS Health Group, in New York City.

Mr. Green, we are going to ask you first to make your statement. I have read your statement, and find it very interesting. I know we will all be interested in hearing what you have to say, because you represent a large number of Americans, and I know you will be speaking for them today. Thank you for coming.

STATEMENT OF JAKE GREEN, WINCHESTER, KY

Mr. **Green**. It is an honor and a privilege to be invited by Senator Pryor to address this Special Committee on Aging. This is in regard to the high prices of medication.

My name is Jake Green, and I am 75 years old. I am retired and living on a fixed income. My problem is that I was diagnosed in the beginning of 1987 as having Myasthenia Gravis. To control my illness, I take 16 pills of Mestinon, 60 milligrams each tablet, each day. That adds up to 500 pills per month.

The price at the time was $65 for 500 pills at the drug store in Winchester, KY.

On January 21, 1988, the price was raised to $72. Then, on July 29, 1988, I found the price went to $106 for the same pills.

I heard about the Myasthenia Gravis Association of Western Pennsylvania, located in Pittsburgh, PA. I was notified by them that I could obtain Mestinon through their pill bank for $40 per 500 by mail. I joined the organization in January 1989.

By June 10, 1989, I was notified by the Myasthenia Gravis Association that some drastic changes had taken place. Hoffman-LaRoche, the manufacturer of Mestinon, had sold the distribution to ICN Pharmaceuticals of California. ICN, the new distributor, had chosen not to offer special contract prices to the chapter pill bank.

Therefore, as of July 1, 1989, the price at the Western Pennsylvania Drug Bank, as well as throughout the whole country, is a great deal more expensive. Now the price has doubled to $87 per 500 pills, which last 1 month. At the drugstore in Winchester, you have to pay $136 per 500 pills. While I was preparing this speech, I was notified that as of December 1, 1989, the price of Mestinon will increase another 8 percent. Adding this to $87 brings the total to around $93.96 per 500 pills, which still last me only 1 month.

When are these increases going to stop, and what is the reason for them? I am not pleading poverty, and I am not asking for charity. But I am very much concerned, because I am at their mercy.

There is no generic drug to take its place since Myasthenia Gravis is a rare neuromuscular disease, for which there is no cure, but Mestinon is the most effective drug to help control it.

I am very much concerned about how one company can control the price to their own advantage, without any regard for an estimated 120,000 to 150,000 people with the same illness that I have.

To be honest with you, I fear the day when I will not be able to purchase the medicine which is keeping me alive. I hope that this information I have given today about the existing problem of unfair drug prices by the pharmaceutical companies can be remedied. Not one of us in this room is immune from any disease.

It should be our right as an American citizen to have available for any illness medicine which will enable us to live out our lives as best, and as humanely as possible.

Thank you for your time and consideration in this matter.

The CHAIRMAN. Mr. Green, thank you for your very eloquent statement before the Special Committee on Aging. All of us appreciate it.

We are going to allow the other members of the panel to make their statements, and there may be a question or two that we have about your particular situation.

Mrs. Leona Bivens of California is 73, and she has Parkinson's disease. For that condition, she must take Eldepryl, a drug that has long been available in Europe. It was recently introduced in the United States at about twice the price that Europeans pay.

We would like to hear your story, and we appreciate your coming, especially from such a long distance.

STATEMENT OF LEONA BIVENS, SEAL BEACH, CA

Mrs. BIVENS. Thank you, Senator Pryor and members of the committee, for asking me to come here today.

I want to tell you about the difficulty that so many of my friends and I who have Parkinson's disease, have, in paying the high cost of prescription drugs.

I am 73 years old and widowed for almost 1 year. I have Parkinson's disease. I have had Parkinson's disease for 13 years. I live alone in a retirement community in Seal Beach, CA. I have a caregiver who comes in 5 days a week, for 4 hours a day.

The caregiver helps me with shopping, bathing, and dressing. She prepares my meals and does my laundry. She is my friend, she helps me by being a sounding board for my problems.

I am ambulatory, but I do not leave the house alone. I have a walker for inside the house, and have borrowed a wheelchair to use outside as needed.

In 1976, when I was 60 years old, I was given a drug called Sinemet, which is a combination of carbidopa and L-dopa. "I was cured," almost as if by magic. It relieved the symptoms which had plagued me for almost a year. These symptoms were slowness of movement and a difficulty in initiating movement, and a resting tremor of my right hand.

I was so grateful. I continued working until I was 68 years old. I worked as a cardiac nurse-technician. This extra time gave me an opportunity to save additional money for my retirement. I felt happy to know that I was able to care for myself.

As is usual with L-dopa therapy, the drug became ineffective. The so-called "L-dopa honeymoon" was over, and I had to look for other drugs to control the symptoms which had returned. I tried many anticholinergic drugs and dopamine agonists, but none worked.

In June 1989, the Food and Drug Administration approved Eldepryl for marketing as an adjunct therapy for those who had had the Sinemet failure. They said that Eldepryl was for use in conjunction with Sinemet. One month ago, my neurologist started me on Eldepryl.

I started to improve, and I continue to improve, but at what cost? I thought I had a good retirement plan, but how long can I pay the druggist's bill?

Before I started taking Parlodel and Eldepryl, my drug bill was 54 cents a day. It has risen to almost $3 a day. That is with the Seal Beach Health Plan which pays 70 percent for prescription drugs, but which I cannot take advantage of if I have to leave the community.

But if I do not have the prescription drug benefit insurance, the cost will go to $9.62 a day. With other prescription drugs, which I must use and need daily, the cost of drugs will go to $3,800 a year.

I have friends who have bought their drugs on the black market (from Italy and Hungary). I have two sons who are police officers, and I've taught them to live by the law. I prefer to live by the law, and I prefer to have the protection of the FDA, so that I know that the drugs are safe and efficacious. I am not sure what they would be if I were to buy them from some other place.

With the recent scandals in the generic drug industry, I am afraid to take generic drugs. However, the Eldepryl and Sinemet do not fall in this category.

I am frightened now, because I am getting to the place where I should not live alone. My son has urged me to live with him. But if I go to live with him, I won't have my prescription drug benefit insurance, and I don't know what I will do. Every day the cost seems to go up—$2.50 is what is projected as the cost of one 5 mg. Eldepryl tablet and the recommended dose, which is safe, is two per day.

But as I continue to take it, they may find out that we need more medication. How will we be able to pay the increasing costs of the drug?

I'm really mad about the price of Eldepryl. Why does Somerset Pharmaceutical Laboratories need to charge such a high price for a drug where to ongoing research is partly subsidized by N.I.H. and where the company gets tax breaks for marketing an "orphan drug", and has exclusive distributorship for 7 years?

These drugs allow us to be independent and to cut down on the amount of long-term care which we might require. Sometimes I think the worst thing that can happen to you is to grow old and depend on other people for your care.

Thank you again for inviting me to speak with you today. We need an advocate, and we are counting on you.

The CHAIRMAN. Mrs. Bivens, thank you very much. We are all very grateful. We know the trip you made was a long and hard one for you. Have you ever testified before a committee before?

Mrs. BIVENS. No, Mr. Chairman.

The CHAIRMAN. We are very grateful that you would come and make this your initial performance.

Let me say to Mr. Green, so you will know, Mr. Green, when you go to your pharmacist to buy Mestinon, don't blame that pharmacist for the cost of that drug going up. That pharmacist there in your home town in Kentucky has no control over that. What that pharmacist is doing is merely having to pass those increases on to you, the consumer, and on to the Government.

But just so you will know, since 1980 the price of Mestinon, the drug that you depend on for your life, has gone up 260 percent, since 1980. I call this immoral.

Mr. Derek Hodel is our next witness. Mr. Hodel is from New York. He wants to visit with us a few moments this morning to tell us about the organization he is involved with in New York, and the prescription drug known as aerosol pentamidine. It sells today for $26 in England; here in the United States it sells for somewhere between $120 and $150.

I think you have an interesting story to tell, and the Committee would like to hear it.

STATEMENT OF DEREK HODEL, EXECUTIVE DIRECTOR, PEOPLE WITH AIDS HEALTH GROUP, NEW YORK, NY

Mr. HODEL. Thank you, Senator.

We brought two display charts. I would like to ask that they be displayed at this time.

My name is Derek Hodel and I am the executive director of the People with AIDS Health Group in New York City. The Health Group is what is commonly referred to as a buyer's club. It was founded by people with AIDS to help people acquire promising treatments that they cannot otherwise obtain.

Consider this drug, aerosol pentamidine, which is generally sold in the United States at a retail price of approximately $150. In England, the retail price for this version of aerosol pentamidine, while medically the same, is $26. Because of the high U.S. price, many of those in need of this treatment simply do without.

Aerosol pentamidine is approved by the FDA as a highly effective preventive of pneumocystis carinii pneumonia, or PCP, which remains the leading cause of death among people with AIDS. Pentamidine is manufactured in the United States by Lyphomed and has been designated by the FDA as an orphan drug.

Because pentamidine is an orphan drug, the FDA must generally wait 7 years after approval of Lyphomed's application to market pentamidine before it approves any other manufacturer's application to market the drug. During that period, Lyphomed can sell pentamidine, which is not patented, without any price restrictions.

According to House committee reports, this "market exclusivity was intended to be an incentive to develop orphan drugs with little or no commercial value." [1] The House committee concluded that "even with the benefits of the Orphan Drug Act, orphan drugs are not expected to be profitable." [2]

As Chart 1 shows, Lyphomed's wholesale price for the drug in 1984 was $25. Since then, as demand surged, Lyphomed has raised its wholesale price almost 400 percent, to $99.54. Lyphomed has refused to reveal the financial basis for its price for pentamidine or its profits on the drug.

Public information, however, strongly suggests that those sales are highly profitable. Analyses project pentamidine sales in the United States of $70 million in 1989 and $100 million in 1990. Thus, profits for Lyphomed. Some people with AIDS, unable to pay the U.S. price, have sought to obtain prescriptions for pentamidine, have them filled abroad, and import the drug.

This process is arduous and difficult, whether undertaken individually, or with assistance from an organization. Lyphomed has complained that it is unlawful.[3]

In September 1989, the Federal Centers for Disease Control report 109,167 cases of full-blown AIDS in the United States. Chart 2 shows that 11,163 of these cases, or slightly more than 10 percent, were men and women age 50 and over. The Health Group does not keep detailed records of its clients, but I offer here my recollection of two persons who need pentamidine.

The woman I will call Carmen is about 50 years old and is a single mother. She carries HIV, the virus believed to cause AIDS, and is a patient at a city hospital clinic. Though Carmen is employed, she is uninsured. Clinic doctors have advised her that she is at risk for PCP, but the hospital is not yet equipped to administer pentamidine. They gave her a prescription for the drug, and suggested that she purchase a $200 nebulizer to administer it at home.

Social workers often advise persons in Carmen's position that if they cannot afford the prescription, they should leave their jobs so that they will qualify for Medicaid. Carmen remained at work, but for 3 months she simply kept the prescriptions in her handbag.

The man I will call Roger is about 63 years old and is employed. Within a few years he will be eligible to retire with a pension. Roger is HIV positive, and while he is well enough to work, his T-Cell count is slow enough to warrant PCP prophylaxis. Roger fears that if he files a health insurance claim for pentamidine, his employer will suspect that he has AIDS and fire him. Instead, Roger has been using his savings to purchase the drug at a pharmacy.

The problems revealed by the pentamidine situation are systemic. Pricing problems have also arisen, for example, with AZT, another orphan drug used to treat people with AIDS. James Mason, Assistant Secretary of Health and Human Services, recently felt compelled to urge publicly that in pricing AIDS drugs, drug manufacturers should be more socially responsible.

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[1] H. Rep. No. 473, 100th Cong., 2d Sess. (1987) (emphasis added), reprinted in 1988 U.S. Cong. & Ad. News 46, 48.

[2] H. Rept. No. 153, 99th Cong., 1st Sess. (emphasis added), reprinted in 1985 U.S. Cong. & Ad. News 301, 306.

[3] Earlier this year, Lyphomed responded to intense criticism by announcing that it would provide aerosol pentamidine without charge to some indigent patients. So far as we are aware, Lyphomed has not announced details of the program or distributed any pentamidine under it.

When drug manufacturers can and do charge exorbitant prices for desperately needed drugs, particularly orphan drugs, for which manufacturers receive special exclusivity, substantial tax credits, and in certain cases development grants from the Government, we think the system has gone radically awry.

Thank you for your attention.

[The charts referred to by Mr. Hodel follow:]

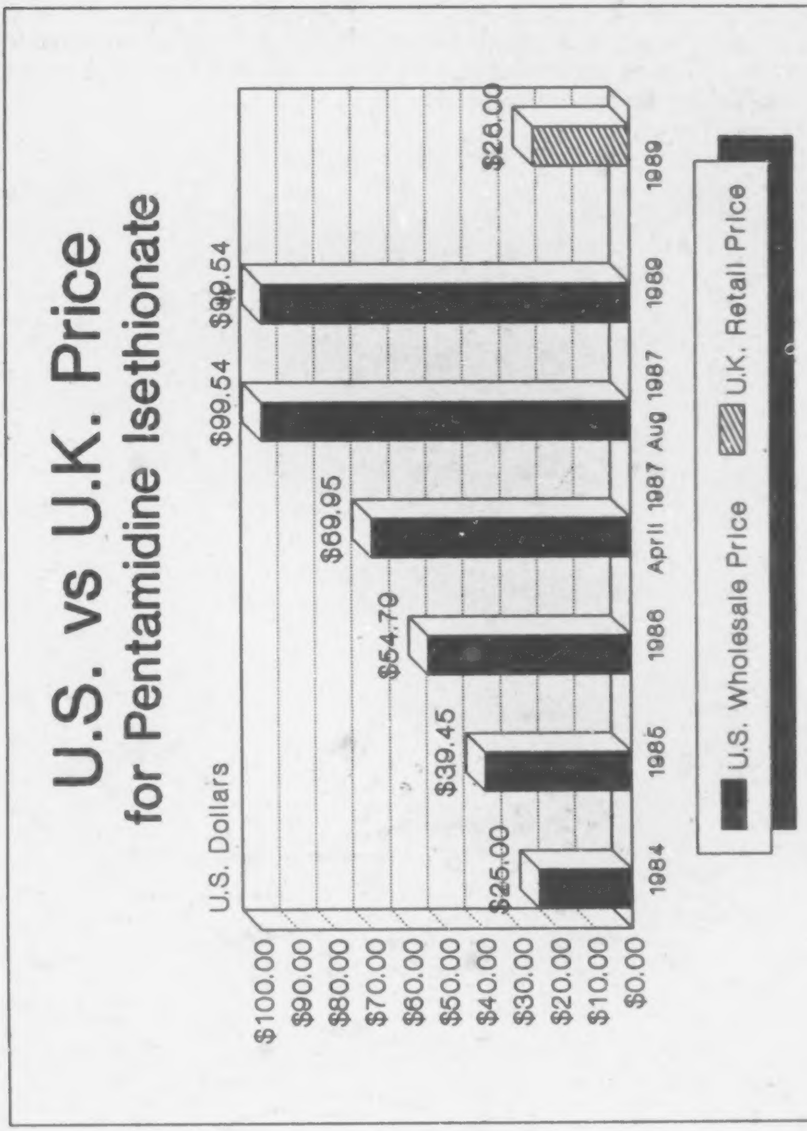
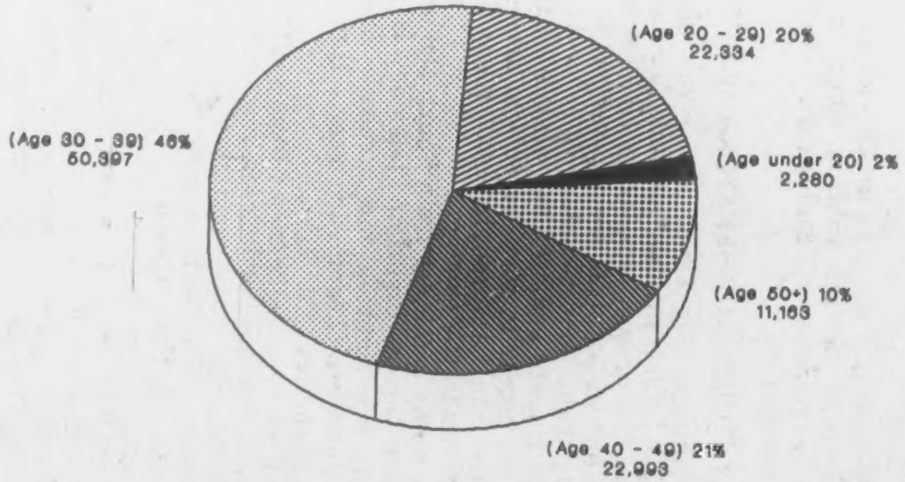

U.S. vs U.K. Price
for Pentamidine Isethionate
U.S. Dollars
$100.00
$90.00
$80.00
$70.00
$60.00
$50.00
$40.00
$30.00
$20.00
$10.00
$0.00
$25.00
$39.45
$54.79
$69.95
$99.54
$99.54
$26.00
1984
1985
1986
April 1987
Aug 1987
1989
1989
U.S. Wholesale Price
U.K. Retail Price

Chart 1

Cumulative AIDS Cases as of Sept. 1989
Age at Diagnosis



109,167 Total Cases
Chart 2

The **Chairman**. Mr. Hodel, thank you very, very much. I would like to indicate for the record that the Committee invited representatives of Lyphomed to testify today. They refused to do so. Perhaps at our informal 1:30 gathering, someone representing that particular company might be present. I doubt it, but I hope they are.

Senator Pressler has asked to make a short opening statement at this point. I think he has another committee appointment, and then I will yield to Senator Bradley for an opening statement.

Senator Pressler.

STATEMENT OF SENATOR LARRY PRESSLER

Senator **Pressler**. Mr. Chairman, I will place my statement in the record, but I did want to say thank you for holding this hearing on the pricing of prescription drugs. It is a subject that I believe needs examination because of its potential to adversely affect the health status of the poor and elderly.

Now is the time to examine the dramatic affect pricing practices are having on access to pharmaceutical services for the aged and poor. This hearing has brought forth many indications of what I think are abuses in the pricing.

There are many examples from South Dakota. A pharmacist who is an inspector for the Board of Pharmacy in South Dakota writes, "Pharmacists are fighting for survival, especially in the small towns, and more are closing each year." He goes on to cite some of the specific examples.

An elderly woman has written to me, she is on a fixed income, and notes that her one medication has increased almost $5 in less than 6 months. She questioned the pharmacist thinking he had made a mistake, it is the pharmaceutical companies, not the local pharmacist, that is the problem.

Another drug has increased by 42.4 percent in less than 2 years. The drug is called Ogen. This is one example that many constituents and pharmacists tell me about in their correspondence. Price increases like this can no longer be tolerated. The effect will be unaffordable drugs for the elderly and poor.

What could possibly be driving the price of drugs upward? I understand the pharmaceutical manufacturers give away millions of dollars worth of prescription medications each year. The cost of promoting a product is passed on to the consumer.

A pharmacist, who worked for a large drug manufacturer, found that the cost of giving one package of four sample pills away was almost the same as producing a bottle of the same pills which could be sold to a pharmacy for $30 or $40.

Mr. Chairman, I think we are seeing abuses in the sale of drugs. I think the price many senior citizens pay are excessive, unexplainable increases. I think that if the companies do not respond with a better explanation that it is time for Congress to act in the area of pricing legislation or antitrust legislation. It may well be that we need new legislation in this whole area.

[The prepared statement of Senator Pressler follows:]

Mr. **Pressler**. I want to thank the Chairman of the Senate Aging Committee for convening this hearing on the pricing of prescription drugs. This is a subject that I believe needs examination because of its potential to adversely affect the health status of the poor and elderly. Now is the time to examine the dramatic affect pricing practices are having on access to pharmaceutical services for the aged and poor. I am pleased that the earlier hearing in June has led to this second hearing on the pricing of prescription drugs.

Pricing practices discriminate against the retail pharmacy, the elderly and the poor. The increasing cost of prescription drugs are a threat to the viability of the small town pharmacy. A pharmacist who is an inspector for the Board of Pharmacy in South Dakota writes "pharmacists are fighting for survival, especially in the small towns and more are closing each year. I am sure I could not sell my store if I had it today. There are a lot of them out there that aren't going to make it." Where will the rural elderly go for medication if the retail pharmacy closes its doors?

The closure of retail pharmacies is only one of the problems that could adversely affect the health status of the elderly. A second is the dramatic price increases that the elderly, who use prescription drugs, are asked to absorb sometime more than once each year. An elderly woman, on a fixed income, noticed that her one medication had increased almost $5.00 in less than six months. She questioned the pharmacists, thinking he may have made a mistake. The pharmacist's comment was that "Abbott Pharmaceutical Company raises their prices twice a year and this cost reflected the last increase." The drug from Abbott is Ogen (OH-jun). The price on Ogen has increased by 42.4 percent in less than two years. This is one example that many constituents and pharmacists tell me about in their correspondence. Price increases like this can no longer be tolerated. The affect will be unaffordable drugs for the elderly and poor.

What could possibly be driving the price of drugs upward? I understand that pharmaceutical manufacturers give away millions of dollars worth of prescription medications each year. The cost of promoting a product is passed on to the consumer. A pharmacist who worked for a large drug manufacturer found that the cost to the manufacturer of giving one package of four sample pills away was almost the same as for them to produce a bottle of the same pills which they could sell to a pharmacy for $30 to $40 for retail sale. That was due to packaging costs, government regulation and distribution by salesman. I question whether the benefits warrant the cost to the public. Could the cost of drugs be reduced by discontinuing this practice?

The practice of competitive bidding and volume discounts has allowed hospitals and other health organizations to obtain a discount on the price of drugs. That is a practice which allows those institutions to distribute prescription drugs at a reasonable price. If this practice is not practical for the retail pharmacists, then other means need to be explored in order to reduce the climbing prices and allow the poor and elderly to continue to have access to drugs that benefit their health.

I would like to make this statement and letters from constituents' part of the record.

Western Hills Home Health CAREQUIPMENT & I.V. Therapy
2929 5th Street, Suite 110, Rapid City, SD 57701
Telephone: 341-CARE • Toll Free: 1-800-658-CARE • FAX 605-341-2273

Dear Senator Pressler:

In response to your letter of August 17, 1989 concerning prescription drug prices. I was pleasantly surprised at the amount of correct information you have gathered. To be honest I did not think anyone had as true a grasp on the facts as you have.

I am a Pharmacist practicing in an independent pharmacy in Rapid City, SD. I have been in practice for 12 years.

The large mail order out of state services are taking a lot of business and money out of the state. The most discourging aspect of this is the fact that some employer's insurance companies require their employees to send for their prescription needs to contracted pharmacies out of South Dakota (IE. Federal Govt. Retire Employees).

Non-profit hospitals are redirecting inventories to connected businesses to be used to supply outpatient needs. The outpatient use should not be allowed , as I understand the Robinson Patman Act.

Since you are aware of the fact that independent pharmacies do not enjoy any of these various discounts you can see the future of the independent pharmacies in rural South Dakota and the potential problems related to health care for all ages. I feel the pharmaceutical manufacturers will have to be regulated before any true discrepancy in pricing will be stopped. They are the one entity that controls the prices. The areas I feel that should be regulated are:

1. Pharmaceutical manufacturers give millons of dollars worth of prescription medication samples each year. These dollars lost must be made up in the prices charged to pharmacies purchasing their products. It is an unnecessary practice that is not only warping the cost of a product but can and has in the past lead to black market drug diversion.
2. Pharmaceutical manufacturers should not be allowed to offer such wide price discounts, period. The fewer exceptions, the fewer loop holes.
3. Pharmaceutical manufacturers should be required to monitor any group receiving discounts to be sure they are not being used or diverted into areas not qualified for these price discounts. If the paper work is so complicated perhaps they will think twice about offering as many discount accounts.

I Thank You for your time and allowing me to share my concerns with you. I hope this letter will show you the type of support you'll enjoy on these topics.

924 No. Union Ave.
Madison, So.Dak. 57042

Senator Pressler:

In response to your letter addressed to So. Dak. Pharmacists: Yes, prices of some prescription drugs are exorbitant. However, the differentiation of acquisition costs to small independent pharmacies relative to urban and large company costs is hardly the reason. I have been on both ends of the spectrum. There is a problem, however, with price discrimination between retail pharmacies vs. "non profit" organizations (e.g.almost every hospital in South Dakota qualifies). There you would find acquisition costs varying up to 99%. The retail pharmacy consumer picks up the stack for the same drugs that are virtually given to these "non profit" institutions.

Another significant factor is the practice of drug sampling by manufacturers. Having worked for the USAs largest drug manufacturer at one time, I found that the cost to the manufacturer of giving one package of 4 sample pills away, was almost the same as for them to produce a bottle of the same pills (#100) which they would sell to a pharmacy for $30 to $40 for retail sale. That was due to packaging costs, government regulation, and distribution (salesmen). Does the benefits warrant the cost to the public? I think not. How much could drug costs be pared if this practice was discontinued? A lot. (The practice also contributes to drug diversion.)

Yes, the exorbitant costs are due to manufacturers prices. The attitude that seems to prevail is "why charge 50¢ per capsule when we could just as well charge the pharmacy $1.50. After all, we don"t have to face the ultimate consumer anyways." There is absolutely NO financial competition among manufacurers.

Larry, that lack of competition leads to another industry problem. What a coincidence that at the same time that the US Senate is finally hinting that an investigation might ensue, an offensive is beginning to discredit all generic drugs. I think it is a result of the original manufacturers scheme "Lets strike fear into the hearts of consumers that generic drugs are no good". I would bet my bottom dollar that the timing is no coincidence. For once, a little competition for drug manufacturers from generice firms, and THEY DONT LIKE IT. Of course there are shady people and shady companies in every field, and those in generic manufacturing should be policed and punished. But there are shady people among PMA (Pharmaceutical Manufacturers Assn.) members also. PMA members simply do not like financial competition and seek to eliminate it.In what other industry besides drug manufacturers, do companies react to competition for their product by raising their prices? DRASTICALLY? When the drug Dyazide went generic, the original manufacturer responded by drastically raising their price. Does that make sense? They must not believe in competing financially. Larry, in my mind, this is the biggest ripoffs in pricing of drugs.

I could go on and on about this topic. But, skimming the surface, this is where a cleanup should begin. I write this for your private information →not for publication. Thanks.

1505 Edgewood Road
Sioux Falls, S. D.
August 16, 1989

Dear Senator Pressler,

I read with interest the article in last Saturday's Argus Leader concerning your plan to ask for hearings on the pricing of prescription drugs. I applaud you for this effort.

It was just a month ago, after having a prescription refilled, that I was angered and upset to find that the cost of this medication had increased almost $5.00 since I had last had it filled in March. I thought this was terribly out-of-line and questioned the pharmacist about a possible mistake in marking the price. He had little comment other than to say that Abbott Pharmaceutical Company raises their prices twice a year and this cost reflected the last increase.

It seems to me that an up-scaling of this magnitude is gouging the customer and is grossly unfair to the consumer whether a senior citizen or younger person. If the trend continues, the escalating cost of good health and staying well will affect every one of us and will become an unaffordable burden to many. What a frustrating and discouraging situation to those who are dependent upon a number of daily medications to maintain healthful living.

1989 AUG [illegible] 3 47

Enclosed is a record of two prescriptions I take daily as "health maintenance therapy". The Ogen (from Abbott) is the drug that has increased so rapidly in price...42.4% in less than two years. This is an incredible amount! The Tenormin shows a 11.1% increase in less than two years; but without a recent jump, I expect the next refill will be more expensive.

I hope these figures will be helpful in your investigation of drug prices to South Dakota consumers. Thank you for your concern in trying to find a solution to this costly and continuing problem. I hope the hearings will produce positive results.

[illegible] two prescription drug medications:

[illegible] Pharmaceutical Company) #100 tablets

[illegible]-18-86	$24.39
[illegible]-02-87	26.51
10-16-87	26.51
2-11-88	28.84
7-03-88	29.93
3-06-89	29.93
7-14-89	34.74

TENORMIN(ICI Pharmaceuticals P.R.,Inc.) #100

10-30-87	44.98
2-11-88	46.55
5-26-88	46.55
12-01-88	47.49
3-23-89	49.99
6-30-89	49.99

Dear Senator Pressler:

Thank you for the opportunity to respond to your study on the high cost of prescription drugs.

I have practiced pharmacy in a variety of settings including a small independent pharmacy, chain store, clinic pharmacy, and hospital pharmacies. It has always amazed me as to the pricing structure provided by the pharmaceutical manufacturers given the type of pharmacy involved. In the retail pharmacy, I usually dealt with wholesale vendors as opposed to purchasing direct from the manufacturer. In the majority of cases, the wholesaler provided a very competitive pricing structure. I did find though that I could never compete with the hospital pricing structure given their advantage as you noted with the Nitro-Dur example. I also noted that hospitals did not pass the savings on to their patients but that the pharmacy helped pay for other services within the hospital setting that did not add to the overall income. An example is patient education. This service is usually provided but no charge is made.

There are two issues that always caused me frustration and I would like to share these. The first is that pharmaceutical manufacturers can always raise their price for whatever reason, but they never have to face the patient who relies on their product. When Pfizer or Upjohn raised the price of Diabenese or Orinase, they did not have to face the patient when the prescription price was raised but I did. This is not an easy task. The second is related to chain store pharmacies such as Osco, Walgreen, Shopko and others. These pharmacies sell many items at cost or at a very small profit margin. Their profits come from other areas within the store and also the high volume of sales. A small independent pharmacy which is a mainstay in many small South Dakota towns needs to make some profit on all items sold in order to keep the doors open.

It is my opinion that your research will discover a variety of inconsistencies in the pricing structure related to pharmaceuticals. This is a multi-faceted problem and the better job you can do of defining it, the better the solution will be.

Again, thank you for the opportunity to voice my opinion.

1989 -5 AM 9:36

Dear Senator Pressler,

Thank you for your letter of August 17 regarding prescription drug prices. The copy of testimony to the Senate Aging Committee which you enclosed indicates that you have an excellent understanding of the problem. As an independent pharmacy owner, I was particularly pleased by your expression of concern for the fate of small independent pharmaci and their customers who are victimized by discriminatory drug pricing.

I urge you to continue to work for a solution to this problem. Discriminatory pharmaceutical pricing attacks the pocketbooks of a far greater number of people in this country than only those who patroni small independent pharmacies. Indeed, the drug manufacturers treat small independent pharmacies such as my own and the nations largest pharmacy chains virtually the same. Thus, regular cash paying customers pay the highest price of anybody, whether they buy their prescriptions from an independent or chain-owned pharmacy. It is important that any legislatio that may evolve to attempt to rectify this problem be presented as being the pro-consumer and pro-senior citizen legislation that it truly is, so that it is not doomed by being incorrectly perceived as some kind of "bail-out" for the nations pharmacies.

With regard to my experience in obtaining fair prices from suppliers I am treated the same as all other retail pharmacies by the nation's large drug manufacturers: I pay the highest of their several prices. The price is not negotiable---I must pay the price they have established in order to obtain the product to fill the prescriptions I am receiving. As you already know, that price is often outrageously higher than that being charged to certain others. It seems to me that the Robinson-Patman Act and Non-Profit Institutions Act need to be re-examined and revisions to protect the American public from price-gouging considered.

Please contact me at any time regarding issues or concerns involving drugs, pharmacy, or any other issue even if not pharmacy-related.

Dear Larry:

I have received your letter of August 17th, and the copy of your message to the senate in the Congressional Record. Great job, just great!

I operated my pharmacy in Belle Fourche for 25 years. I then retired and sold it to Ron and Marilyn Schwans formerly of Hoven. That was six years ago. I am now the pharmacy inspector for the Board of Pharmacy, a relief pharmacist, and an after dinner speaker. My area as the inspector is the total West River area, so I get into every pharmacy in the West River a couple of times a year. Believe me, Larry, all of them are talking about you and how you picked up the ball and ran with it on the subject of price discrimination in pharmacy product distribution from manufacturer to retailer.

Really, Larry, it's very sad! These pharmacists are fighting for survival, especially in the small towns and more are closing each year. I am sure I could not sell my store if I had it today. There are a lot of them out there that aren't going to make it!

Everything you said was exactly right, Larry, and you said it all. All these pharmacists really want is a chance to compete on an equal basis.

When Nils Boe was governor he spoke at a pharmacy convention. He said, "when I go into a small town in So. Dak I look at two things, the bank and the drug store. If both of these are modern and doing business, this is a good town. If the drug store and the bank are dead, the town is dead!" That's the way it really is, Larry, and a lot of our So Dak towns are dead because the drug store is not making it.

I was working "relief" for Lou Thompson in Faith a couple of times when you came in to see Lou. You and I have visited at the Rx counter. I have my photo with you and Bob Dole when he was with you at the Alex Johnson Hotel during the primary. Your doing a great job for So. Dak, Larry!

Again, I want to say thank you for your efforts to keep the small town pharmacists. I hope we get some action!

August 20, 1989
1169 Lookout Lane
Rapid City, SD 57701

Dear Senator Pressler:

In way of introduction, I would like to introduce myself. I am a practicing pharmacist and First-Vice President of the S.D. Pharmaceutical Association. I am writing to commend you for your efforts concerning the problems with prescription drug pricing. I know that Marilyn Schwans and Galen Jordre have been in contact with you and I felt your testimony at the Senate Aging Committee hearing was accurate and to the point.

The alarming part of all of this, was that I heard from a customer that residents of South Dakota pay 30% more for their prescriptions than any state in the nation. And perhaps if you read the lead-in paragraph of the Argus Leader concerning your probe (and did not finish the article!) you would agree that the article is mid-leading. I would hope that our customers will not begin to look elsewhere for their medications (mail-order houses in other states!) etc.

We at Boyd's Drug Mart in Rapid City are a highly competitive drug store. We compete with chain drug stores such as Shopko, Albertson's, and Safeway. For example, Shopko was selling Tagamet 300mg at $7.21 under cost! We attempt to match them, but we lose $5.77 on each prescription for #100. Albertson's sells theirs for $53.89 per #100 so they actually make money! You can thus see the wide disparity of prices in the prescription drug industry. Perhaps the Association can spearhead an effort to pass a law similar to the liquor industry, that no product can be sold below its cost. This would eliminate unfair competition and prevent pharmacy shopping, which has been proven to be detrimental to a patient's health.

Thank you for your attention to the problem, and please continue your efforts. Please let the association know if it can be of any assistance at any time.

Meditrol® Inc.
AUTOMATED MEDICATION SYSTEMS

1989 SEP [illegible] 2 06

Dear Senator,

Your concern about the continued rise in the cost of medication to our senior citizens, as well as the rest of the small drugstore population, is one shared by me as well. For 25 years I was involved in a clinic pharmacy in Rapid City. Since that time I have developed a company here that makes an automated drug distribution system for hospitals.

In my years in retail pharmacy, I decided to do something about the high cost of drugs to our rural population by starting a company that combined a number of small retail drug stores into a buying group. We called it Medcor. At that time, we bid drugs from major suppliers. We could buy 1000 capsules of an antibiotic, that normally cost individual stores $40.00, sell it to the store for $12.50 and still make 15% profit.

Once this process was started the major manufacturers had a meeting here in Rapid City on ways to put us out of business. The stores were offered free drugs if they would stop supporting our operation and various other measures which culminated in my suing 7 of the major drug companies. The suit was settled out of court.

I only bring this up in that there is a way to bring prices down, but it requires the small stores to join together to provide the buying power. That is the only thing that the drug companies understood. However we pharmacists are much like the ranchers who will step in and help anyone in trouble, but will never do anything together for our mutual benefit.

In this respect, laws that would require like bids, on like quantities, would be helpful. Currently the law divides the buyers into groups (i.e., small retail stores, larger retail stores, chains, small hospitals, large hospitals, etc.) This division gives the drug companies ways to circumvent the real purpose of the Robinson Patman Act.

To speak in the defense of the drug companies, I feel we must always continue research and that to encourage this we must allow the patent protection that allows a profit on the new drug that is developed. It is impossible to state that a price is too high, but perhaps the length of the patent is too long.

Now to speak to the growing number of mail order operations:

Mail orders are usually for long term medications. The calls in the middle of the night for a pain killer are never filled by these operations. Only the local pharmacist delivers this kind of necessary service and they are being put out of business.

May I suggest the following:

1. Encourage pharmacists to band together to provide buying power.
2. Help them finance the project through SBA.
3. Eliminate the "group" designations in Robinson-Patman and change them to "quantity" purchased.

It will be a long battle, but the purpose is certainly just. Persevere! If I can be of any assistance, please give me a call.

Dear Senator Pressler,

I am responding to a letter that you sent regarding prescription prices. As a pharmacist who has worked in hospitals, retail stores and in mail-order pharmacy, I would like to present some of my views.

It is true that pharmacies with higher volumes of business are sometimes able to buy at better prices, however, the few percentages saved are hardly the reason why the prices they charge are lower. South Dakota has many rural pharmacies who do not have a lot of volume and therefore many times are forced to sell their prescriptions at much higher prices in order to do business.

I feel that there are two primary reasons where a difference can be made:

(1) If possible, I would like to see a government body appointed to approve how much a manufacturer is allowed to charge for newly developed products. There should also be some regulation regarding how often and by how much they are to be allowed to raise prices on existing drugs. There is hardly a day that goes by when price increases do not occur. This is the MANUFACTURER's fault, not the pharmacist or pharmacy who sells the medicine. We have no choice. Some prices are outrageous and I very much empathize with consumers, especially the elderly.

(2) The other area where a difference could be made, but would probably be harder to do so, is in the preferential pricing given to hospitals. This in many ways increases the retail price in order to support the very inexpensive prices that hospitals are given. It is definitely not fair, and again it all goes back to the manufacturer. It is no wonder that stocks in major drug companies are good to be in-- they have no limit to what they can charge for their product, and the customer has no choice many times if there are no generics available.

You no doubt have heard many negative things about mail-order pharmacy. I work at Tel-Drug, which is the only mail-order pharmacy in South Dakota and only one of many in the country. We feelthat by keeping some mail-order pharmacy in the state we help to enhance our state's economy instead of losing the business to out-of-state mail order services.

I do the majority of ordering of prescription drugs for the operation and I can tell you that we do not buy at prices which are significantly lower than any other pharmacy in the state can get. I would be more than happy to show you our ordering system and operation in general. Many South Dakota pharmacists do not like our business because we take away their business and so you will hear negative things from them. I would probably be the same way if I were in their shoes. However, business involves competition and that is the way our country runs-- and the ultimate winner is the consumer. The majority of our customers are elderly in South Dakota and they love us for two major reasons-- we save them money and deliver to their door via the mailbox. When you are old and are not able or willing to drive 30 miles to the nearest drug store, you really appreciate the savings of mail-order, as our cutomers do. Ask them.

In closing, I would invite you to call me at home (361-5405) or arrange a time which would be convenient and I would be more than happy to share more of my views or give you a tour of Tel-Drug. I would love to help you with your effort in these areas, because it is a very timely issue for all of us, but especially the elderly.

RAPID CITY REGIONAL HOSPITAL

Thank you for your recent letter concerning your activities at the Senate Aging Committee hearing on prescription drug pricing and an invitation to comment.

My perspective is that of a person who has a graduate degree and 15 years of experience in the hospital pharmacy arena. Drug prices are of critical importance to my department and the hospital. They are collectively the largest budgetary expense item in the department. Expenditures for drugs in today's 300+ bed hospital can amount to several million dollars annually. I have several brief comments:

1. The generic drug industry is very important to hospital pharmacy as a method of cost containment. It is important though that both the public and the medical profession be assured of quality of generic products.

2. The continued ability of hospitals to obtain "non-profit" or "own use" pricing is critical in holding the line on costs particularly since Medicare/Medicaid reimbursement is many times inadequate. The difference in price between a competively bid multi-source drug product and the list price of the same product purchased at wholesale is several fold. In a department with a $1,000,000+ drug budget, a return to single-tier pricing could be catastrophic. This is no less of an issue for the small rural hospital.

3. It appears to me that perhaps the most important single issue relating to recent drug price increases is the maintenance of the current drug patent laws which enable manufacturers to retain exclusivity for the patent period. The health care industry is in a sense held hostage by this market domination of patented products.

4. The issue of substantial price breaks to non-profit entities by manufacturers in order to build brand prestige, etc., is a non-issue in my opinion. An interesting example is Tylenol. McNeil Consumer Product Division has for years given very significant price reductions to non-profit hospitals as a means of building brand recognition and prestige for Tylenol products. We at Rapid City Regional Hospital purchase and use the equivalent of 5 bottles of 100 tablets per week. If we were to assume that each drugstore (15 listed in Rapid City Yellow Pages) and grocery/convenience store (25 listed in Yellow Pages) were to sell an equal amount, we see that the closed-market segment of sales amounts to a mere 2% at most - a figure that one would hardly think would drive regular wholesale prices substantially higher.

5. The volume purchase discounts that chain pharmacies utilize are not unique to health care. Tell me that I pay the same price for a new Chevrolet as Avis does. Volume discounting is a part of a capitalistic society.

SD SHp
South Dakota Society of Hospital Pharmacists
P.O. Box 7017 • University Station • Brookings, SD 57007 • (605) 688-6197

Dear Senator Pressler:

I appreciate receiving a copy of your testimony at the Senate Aging Committee hearing. I am the Pharmacy Director of Mobridge Regional Hospital in Mobridge and am the current President of the South Dakota Society of Hospital Pharmacists. From a personal and organizational perspective, I would like to present the community hospital side of the prescription drug pricing disparity.

The advent of DRG reimbursement several years ago has put a cap on the ability of the rural hospital to generate revenue. At my hospital, about 75% of patients are Medicare or Title-19 recipients and the hospital is paid a fixed fee for treating these patients. If that fee is not providing an acceptable margin of profit, or possibly not even covering costs in many instances, attempts to reduce costs must be made. For the pharmacy, one of the hospital's major revenue sources, the primary tool we can use is buying group purchasing power and related bid pricing. Even the effectiveness of this tool has been dampened by inclusion of actual costs of drugs to hospitals in DRG formulas. The Federal Government was not ignorant of pricing policies when putting together reimbursement figures! If all preferential and bid pricing was suddenly eliminated, our hospital along with most other rural institutions would not survive.

I do not favor exhorbitant pricing to the independant pharmacist, but extreme caution must be exercised in finding a solution to this problem. I feel Congress may be able to legislate better regulations and laws governing "nonprofit" status, but legislating across-the-board equivalent pricing (the goal of the Pharmacy Freedom Fund) would be devastating. I have many friends who own independant drug stores and I know they are fighting some unfair battles. Chains and mail-order, along with HMO's, threaten their livelihoods. However, they have chosen their situations and must use the tools they have at their disposal to fight the battle. The local hardware store and corner grocery are fighting similar battles and use convenience and personal service to establish successful businesses.

Please don't interpret my opinions as being anti-independant pharmacy. On the contrary, I feel the local drug store is absolutely essential to the public's health. If means to provide more fair pricing can be found, I am all for it. If this is at the expense of the demise of rural hospitals, all will suffer. The Federal Government's costs of health care will skyrocket to unforseeable levels.

Thank you for considering all sides and consequences of this issue before proceeding.

I am responding to the questions and comments you made in a letter sent to me on August 17, 1989. I do not claim to have all the answers. However, I will try to share my views and opinions with you.

One question you mention involves the value of the prescription drugs we are buying. Prescription drugs are valuable in actually keeping the costs of health care down, primarily through preventive medicine and also by promoting a person's wellbeing. One study I read suggests that prescription drugs only account for about 7 percent of the total costs of health care. Considering this, I believe that the cost of prescriptions is a real bargain.

Another question you discuss is that of the drug benefits in comparison to their costs. It would be difficult to put a dollar value on saving a life or improving the quality of a person's life. For an issue of this magnitude of importance I do not think the cost of prescription drugs should be the primary concern.

On the issue of Medicare paying a fair price, I wish I knew the answer. I do know that the price paid in South Dakota for Medicaid patients, basically cost plus $4.25 would be a bare minimum. $4.25 is not a very significant amount to make on a forty dollar prescription, for instance; so I certainly feel this would be more than fair for the government. Regarding fairness to the pharmacies, I am most concerned about the extra time that will be involved and also the computer expenses which will be a part of the new Medicare system. Pharmacies, in order to keep in operation will need to be reimbursed for this increased time spent on required counseling and computer lag time, and more importantly for the computer system whether on a volume basis or possibly on a per prescription basis. I am worried that the new Medicare system might force most small independent retail pharmacies to close due to the enormous number of elderly persons involved and also due to inadequate reimbursement. Increased numbers of third party programs are a major factor contributing factor for low profits. I hope to own a business one day; however, I doubt it will be a pharmacy.

Discriminatory pricing as you mention is a major problem. Perhaps if all pharmacies were charged the same prices, the overall cost to the patient might go down, particularly in the retail setting. If retail pharmacies could purchase drugs for as little as hospitals and HMOs I can assure you that the average cost of each prescription would be lowered substantially, I would estimate as much as twenty dollars less per prescription. You mention your findings that smaller pharmacies are charged more than larger ones in more populated areas. I have not found the community size to be a factor; a single independent pharmacy in Hudson, for instance, is charged the same as one in Sioux Falls. The price discounts I have seen are given to pharmacies in which two or more are owned by the same operation. The more stores owned, the greater the discount given by the wholesaler. The savings, however, to these pharmacies is rarely passed on to the customer.

Another problem, even with the tighter regulations, is abuse of physician samples. I think that if fewer samples were available, perhaps the manufacturers could reduce the price charged to the wholesaler. Persons with the greatest need are generally not the ones receiving the samples anyway.

To learn why prescription drugs are so expensive, one must not overlook the drug manufacturers. Drug development is a very expensive, time consuming process which cannot promise success. Thousands of chemicals are tested in search of one that is promising. Generally, it takes greater than $90 million and between seven to ten years before the FDA approves a drug. Currently, an investigational new drug must show that it is safe and effective in both test tubes and animals before going through three clinical trial phases in humans. Only about twenty percent of all new drugs tested pass the three phases and finally are approved by the FDA. Pharmaceutical manufacturers spend an average of 15 percent of their profits on drug research. Perhaps they could better explain to you why the prescription drugs are so expensive.

Another area of concern is if Medicare requires generic use as is the case with Medicaid. Federal law requires that I dispense a brand name product when a physician signs on the "dispense as written" side rather than the "substitution permitted" side on the prescription blank. However, Medicaid will only pay the generic price unless the doctor writes in his/her own writing, "brand medically necessary," something I have never once seen. This contradicts the legal requirement. If I dispense a generic for a "dispense as written" Medicaid prescription, I am breaking the law; however, if I use the brand name product I must suffer a loss financially. This hardly seems fair.

In general, I do believe in generic substitution. However, all generics are not equal to the brand names they copy. Certainly a generic product can be sold for less since the [illegible] development is much less. Currently, a generic drug does not have to be proven safe and effective by the FDA; it only has to prove that its bioavailability and bioequivalency is similar to that of the brand name product, the latter two factors simply meaning that the generic drug gets to its body site and acts as efficiently as the brand product. I am glad to see that the government is finally cracking down on generics, as seen with the latest generic recalls. There are certain generics I would never personally take and consequently [illegible] to patients, even those with Medicaid or the future Medicare. I wish the pharmacist could seek reimbursement for brand name products for which [illegible] there are no exact generic equivalents, for example, Premarin, Theo-Dur, Dilantin, and Lanoxin.

I hope that I have given you more understanding of [illegible] viewpoint as a retail pharmacist. If I can be of [illegible] in the future, please let me know.

Dear Senator Pressler

In reply to your request for information relative to charges for Prescription Drugs.

I normally get a Prescription for 12 Prednisone tablets which is quite cheap. The druggist at Highmore charges 4^{50} for what he calls the "Computer cost"

I believe this to be excessive as I can get this same Prescription Fill any where else for prices that vary from 1^{50} to 2^{00}.

1989 NOV 30 PM

Dear Senator Larry Pressler:

I whole heartedly support your concern and involvement in regard to getting something done about the high cost of prescription Drugs. I firmly believe the percentage of profit markup on drugs is completely out of line compared to what other States charge. Our elderly citizens are the ones who suffer on these excessive charges. Many of the senior Citizens who I associate with continually complain of the high charges on their drugs and medicines which they must purchase. Thanks for all your good work you are doing as our U.S. Senator you certainly keep your constitutents in mind and in your concerns.

WEBER PHARMACY
P.O. Box 478, Marion, So. Dak. 57043 • Phone 648-3751
We Aim To Please!

8-25-89

Dear Larry,

I would have liked to have come to one of your meetings in S. Dak. ,but I am sure you realize how difficult it is when you are the only Pharmacist in the store and community it is almost impossable to get someone to fill in and if you do it is very exponsive.

I am grateful that you are helping look into the problems of differential pricing as it is a bothersome one for most of us in retail Pharmacy. especially the smaller ones that do not have a gigantic volume. We are supposed to compete with the Walmart,K-mart and now even so called non-profit Hospitals operating Retail Pharmacies. It is difficult to gather proof of what is goning one but I know these type Pharmacies buy at a much lower price than we do. Their are a lot of Companies that have special Hospital prices. I have goten invoices my mistake and saw some prices for example they purchase bottles of 1000- Tylenol for less than we can buy 100s. and I am told that the V.A. buys nitorglycorin transdermal patches for about 1 or 2 cents each and they are costing us over $1.00 each.

I realise also that the elderly or should I say some of the Elderly have a very low income and need and desearve the lowest prices but I am also informed that some Companies such as SKF soll products direct to like The AARP assn at about ½ what we pay so it puts us in a very bad light when we try to compete with this mail order type Pharmacy which is very poor medically anyway because the patient has no direct contact with the Pharmacist whoe fills their medication in order to ask questions about side effects and reactions with drugs they may already be taking.

We also have to put up with situations like the one I wrote to you about before whereby Postal employees in small towns like ours are required to order their prescriptions by mail for Phoenix arizona etc and we small busnessman do not even get a chance to compete.

Thankyou for your consideration of some of our problems and the concern of the population as a whole and especially the elderly of getting the best care at the most economical prices.

AFFILIATED INDEPENDENT DRUGGISTS INC.
(605) 225-0416 • 213 E. Railroad Avenue • P. O. Box 116 • Aberdeen, SD 57402-0116

August 15, 1989

Dear Senator Pressler:

As a South Dakota citizen concerned about the horrendous manufacturers price increases on pharmaceuticals and as the manager of a buying group of independent pharmacies, I read your speech in the July 31, 1989, Congressional Record with great interest and appreciation. It is indeed gratifying to independent pharmacists to know that the U.S. Senate is made aware of the facts concerning the huge price increases in pharmaceuticals. I would like to, on behalf of all of the independent pharmacies in our organization, express our thanks to you for your support in maintaining our presence and maintaining health care coverage in our rural communities.

A point that would indicate the support you will receive in your stand to eliminate discriminatory pricing of pharmaceuticals. At our annual corporate meeting in June 1989, AID, Inc. and its individual members gave and pledged financial and active support to the Pharmacy Freedom Fund (PFF). PFF is a voluntary national organization of independent pharmacists dedicated to accomplish the end of discriminatory pricing as you discussed in your speech.

By a copy of this letter I am asking PFF to supply you with the statistical data accumulated to date and in the future showing the facts of pharmaceutical discriminatory pricing.

Again, Senator Pressler, we appreciate and thank you for support you are giving us on this problem.

[illegible] Drug
BOX 787
BELLE FOURCHE, S. D

AUGUST 15, 1989

DEAR SENATOR PRESSLER,

CONGRATULATIONS ON YOUR STATEMENT OF JULY 18,1989 TO THE HEARING OF THE SENATE SPECIAL COMMITTEE ON AGING, ON THE PRICING PRACTICES OF PHARMACEUTICAL MANUFACTURERS.

YOU DID AN OUTSTANDING JOB OF DEFENDING THE INTERESTS OF INDEPENDENT PHARMACISTS IN SOUTH DAKOTA. I CANNOT GIVE YOU ANY NEW INFORMATION, HOWEVER, I CAN SAY THAT INDEPENDENT PHARMACIES ARE HAVING FINCANIAL PROBLEMS IN SOUTH DAKOTA, AND VERY FEW ARE SALABLE OPERATIONS TODAY.

MY WIFE AND I OPERATED SCHWANS DRUG IN HOVEN FOR 13 YEARS AND ARE JUST COMPLETING OUR 6TH YEAR IN BELLE FOURCHE. IN 1983 WE SOLD A VERY PROFITABLE STORE IN HOVEN TO JUDY BROWN. JUST LAST MONTH JUDY BROWN WAS FORCED TO CLOSE THE PHARMACY IN HOVEN. (THE STORE IS STILL OPEN AS A SUNDRY STORE). THIS REALLY BOTHERS ME BECAUSE FOR 13 YEARS THAT STORE PROVIDED OUR FAMILY WITH A COMFORTABLE LIVING. JUDY IS AN EXCELLENT BUSINESS PERSON BUT WAS NOT ABLE TO COMPETE WITH THE MAIL ORDER FIRMS. HER DOCTORS DO NOT ALLOW GENERIC SUBSTITUTION. JUDY HAD TO USE EXPENSIVE BRAND NAME DRUGS AND THE LONG AND SHORT OF IT IS THAT SHE COULD NOT GET AN ADEQUATE FEE TO STAY IN BUSINESS IN HOVEN.

SIX YEARS AGO WHEN MARILYN AND I PURCHASED CLIFF THOMAS DRUG IN BELLE FOURCHE FROM RETIRING CLIFF THOMAS THE GOAL WAS THAT I WOULD RUN THE STORE AND MARILYN WOULD BE AT HOME WITH THE FAMILY AND JUST RELIEVE ME FOR NOON HOURS, HAIR CUTS, ETC. TODAY I RUN THE STORE ALONE AND BROWN BAG IT--MARILYN IS WORKING AS A PHARMACIST FOR FORT MEADE AND WITH BOTH INCOMES WE ARE STAYING AHEAD OF THE BILL COLLECTORS! OUR SALES VOLUME IS UP, I FILL MORE THEN THE AVERAGE NUMBER OF PRESCRIPTIONS OF SOUTH DAKOT INDEPENDENT PHARMACIES AND WE WILL SURVIVE. THE DISAPPOINTING THING ABOUT OUR DRUG STORE IS THAT TODAY WE COULD NOT SELL IT BECAUSE NO YOUNG PHARMACIST COULD PAY FOR THE HUGE INVENTORY AND STILL EARN A LIVING. IF I WERE RETIREMENT AGE I WOULD LIQUIDATE IT. THIS PROBABLY IS NO GREAT LOSS FOR T PEOPLE OF SOUTH DAKOTA BECAUSE BELLE FOURCHE HAS TWO OTHER PHARMACIES. HOWEVER; THERE ARE SEVERAL ONE DRUG STORE TOWNS IN SOUTH DAKOTA THAT ARE GOING TO BECOME ANOTHER HOVEN.

Dear Larry,

Drug manufacturers have always Had 15 deferent prices down through the years. They have different schedules for small retailers,wholesalers, large chains, hospitals & hmo's, and federal and state government. Government usually gets the very lowest price because they require competitive bids each year. As an example an item that costs the small retailer about $35.00 wholesale will cost the government about $5.00

Hospitals and hmo's probably get the next best price after the government. Large retail chains and wholesalers receive volume discounts on truck-load orders shipped to their central warehouses. Small independent retailers, becaus of lower volume, must order from regional wholesalers and therefore pay the highest price for the same item. Most S.D. pharmacies fall into this category.

Merck Sharpe & Dohme company is the only manufacturer to my knowledge that has a policy of one price to all regardless of volume. Whether this applies to govt. bids, I do not know. If all manufacturers and wholesalers would have this polic small stores could be competitive with larges chains and mail order houses in rura america

The latest threat to small town drugstores are the medical insurance companies and mail order houses. Some insurance companies demand their clients send their prescriptions to the company owned pharmacy or they won"t pay anything. Mail orde houses such as the pharmacy service of AARP are taking a toll also. They promise lowest prices To all senior citizens. With these thoughts in mind, its hard for me to believe small town stores will be around much longer.

I would be interested in any comments you may have on this issue.

Hopefully next time I will be able to locate my own paper to write on.

The **Chairman**. Senator Pressler, thank you.

Senator Bradley.

STATEMENT OF SENATOR BILL BRADLEY

Senator **Bradley**. Mr. Chairman, I don't have an opening statement.

The **Chairman**. Thank you for being here, Senator Bradley. If you have any questions, we are going to have a short questioning period in a moment. I already mentioned the price escalation of the drug that Mr. Green is taking.

I would like, if I might, also tell Mrs. Bivens that in 1964 Eldepryl was discovered in Hungary and has since been marketed there. Today, a U.S. pharmaceutical firm merely purchases Eldepryl from the Hungarian company and sells it in the United States.

In Italy, one pill of Eldepryl is 41 cents, per pill. In Canada, it is $1 per pill. In the United States, it is $2.38 per pill. We are shortly going to have some explanations as to why the drug prices in our country are so much higher than they are in almost any other area of the world.

Let me if I might just ask a couple of questions, and then I will yield to Senator Heinz.

Tell me, if you will, Mr. Hodel, about the so-called "give-away" program of aerosol Pentamidine to indigent victims of AIDS. Is this program working?

Mr. **Hodel**. Lyphomed has been talking to the community about creating an indigent patient program for some months, beginning at the point when the drug was approved for aerosol use in June. Since that time, they have not formalized the details of the program in any significant manner as far as I am aware. They are close to doing so, they say, but we are not yet aware of any distribution of the drug.

They have indicated that they intend to give drugs away to community-based, not-for-profit clinics, and allow those clinics to decide who is indigent and therefore who is entitled to the drug. We are aware of community-based clinics all over the country who have written to Lyphomed requesting such assistance, but are not yet aware of any receiving such assistance.

I admit that we are somewhat dubious about Lyphomed's intentions. The announcement of the indigent patient program followed considerable media attention to the importation of a competitive product from England. So we viewed it largely as a media ploy.

The **Chairman**. How many of the AIDS victims that you know of are ordering their pentamidine from Europe?

Mr. **Hodel**. It is difficult to estimate, although I would guess that it is no more than a few hundred. It is a very difficult process to import a medication from any other country, so most people just aren't aware of it.

The **Chairman**. I don't think there is any dispute as to the exact sameness or similarity between the pentamidine produced in England and the American equivalent, manufactured by Lyphomed. Lyphomed, as I understand, protested to the Food and Drug Administration, and asked the Food and Drug Administration to have

Customs officers stop and seize all of this English-made drug coming in to our borders.

Mr. **Hodel**. To the best of my knowledge, it is.

The Chairman. We have cables to that effect, and I am going to place those cables in the record,[4] because I think it shows the extent a drug manufacturer will go to to basically protect their turf and their monopoly, as given to them by the Food and Drug Administration, or under the laws of this country.

The **Chairman**. We appreciate what you have had to say. I am going to yield. We have a large number of Senators here. I wonder if we could invoke the 5-minute rule, and we will yield to Senator Heinz for 5 minutes of questions.

Senator **Heinz**. Mr. Chairman, thank you very much. I am going to ask unanimous consent to submit Senator Wilson's statement for the record, if you please.

The **Chairman**. Without objection.

[The prepared statement of Senator Wilson follows:]

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[4] See appendix 6, p. 628.

— ASK TO SUBMIT STATEMENT, THE BAKER/ISENBERG LETTER, + NEW YORK TIMES ARTICLE FOR THE RECORD —

THE HONORABLE PETE WILSON
NOVEMBER 16, 1989
SENATE SPECIAL COMMITTEE ON AGING
PRESCRIPTION DRUG PRICING

MR. CHAIRMAN, I AM PLEASED THE SENATE SPECIAL COMMITTEE ON AGING HAS THE OPPORTUNITY THIS MORNING TO EXPLORE PROBLEMS AND SOLUTIONS RELATING TO PRESCRIPTION DRUG PRICES. I BELIEVE THE COMMITTEE'S JULY HEARING WAS EFFECTIVE IN OUTLINING THE DIMENSIONS OF THE PROBLEM OF ESCALATING PRESCRIPTION DRUG COSTS. TODAY WE HAVE THE CHANCE TO EXAMINE PRIVATE SECTOR EFFORTS TO NEGOTIATE LOWER PRESCRIPTION DRUG PRICES AND TO CONSIDER THE APPLICATION OF SUCH STRATEGIES TO THE PUBLIC SECTOR.

AS WE LEARNED IN JULY'S HEARING, THE STEADY AND CONTINUED GROWTH IN PRESCRIPTION DRUG COSTS IS OF GREAT CONCERN TO THE PRIVATE AND PUBLIC SECTORS. AT THE TIME OF THE HEARING THE ISSUE HAD PARTICULAR REVELANCE TO THE FEDERAL GOVERNMENT AS WE PREPARED TO IMPLEMENT A COMPREHENSIVE OUTPATIENT PRESCRIPTION DRUG PROGRAM FOR ELDERLY AMERICANS UNDER THE MEDICARE CATASTROPHIC COVERAGE ACT.

WHILE THE ULTIMATE DISPOSITION OF THE CATASTROPHIC ACT REMAINS UNCERTAIN, IT IS CLEAR THE DRUG BENEFIT WILL BE ELIMINATED. HOWEVER, THE CONTINUED ESCALATION IN PRESCRIPTION DRUG PRICES REMAINS COMPELLING AND RELEVANT TO THE FEDERAL GOVERNMENT FOR A VARIETY OF REASONS, NOT THE LEAST OF WHICH IS MEDICAID SPENDING ON PRESCRIPTION DRUGS.

IN MY STATE, PRESCRIPTION DRUGS REPRESENT THE FOURTH LARGEST CATEGORY OF SPENDING IN THE MEDI-CAL PROGRAM, AS WE CALL MEDICAID IN CALIFORNIA. STRIKINGLY, PRESCRIPTION DRUG EXPENDITURES HAVE DRAMATICALLY OUTPACED OTHER SERVICES OF THE MEDI-CAL PROGRAM, JUMPING 150 PERCENT SINCE FISCAL YEAR 1978-79 WHILE ALL OTHER MEDI-CAL SERVICES ROSE 50 PERCENT.

MR. CHAIRMAN, I UNDERSTAND YOU REFERRED IN YOUR OPENING REMARKS TO LEGISLATION OFFERED IN CALIFORNIA, A.B. 2148, BY ASSEMBLYMAN BAKER THAT AUTHORIZED THE CALIFORNIA DEPARTMENT OF HEALTH SERVICES TO NEGOTIATE REBATES FROM MANUFACTURERS OF SINGLE SOURCE DRUGS. I WOULD REQUEST, MR. CHAIRMAN, THAT THE LETTER PROVIDED THE COMMITTEE BY ASSEMBLYMEN BAKER AND ISENBERG REGARDING THIS MEASURE BE MADE PART OF THE RECORD.

THE ASSEMBLYMEN'S LETTER NOTES THAT THE MEDI-CAL PROGRAM PAYS OVER $130 MILLION EACH YEAR FOR SINGLE SOURCE PRESCRIPTION DRUGS, FOR WHICH THE STATE PAYS WHOLESALE OR "LIST" PRICE. IN PAYING LIST PRICE FOR THESE DRUGS, MEDI-CAL RECEIVES NO DISCOUNTS, SPENDING BETWEEN 20 AND 80 PERCENT MORE THAN OTHER MAJOR PUBLIC HEALTH PROGRAMS SUCH AS THE VETERANS ADMINISTRATION. SIGNIFICANTLY, MR. CHAIRMAN, AS YOU NOTED IN YOUR OPENING REMARKS, BY AUTHORIZING THE NEGOTIATION OF PRESCRIPTION DRUG PRICES, ASSEMBLYMAN BAKER'S LEGISLATION WOULD HAVE RESULTED IN SAVINGS TO THE FEDERAL GOVERNMENT AND THE STATE OF CALIFORNIA IN THE AREA OF $40 MILLION.

WHILE IT IS DISCOURAGING THAT THIS MEASURE WAS ABLE TO MUSTER ONLY FOUR COMMITTEE VOTES IN THE FACE OF INTENSIVE LOBBYING ON THE PART OF THE PHARMACEUTICAL INDUSTRY, I AM ENCOURAGED BY EFFORTS BY THE CALIFORNIA DEPARTMENT OF HEALTH SERVICES TO ENTER INTO DISCOUNT CONTRACTS WITH DRUG MANUFACTURERS. IN LIGHT OF INCREASINGLY CONSTRAINED MEDICAID BUDGETS AND ESCALATING PRESCRIPTION DRUG COSTS, I AM CONVINCED THIS IS THE DIRECTION ALL STATE MEDICAID PROGRAMS MUST TAKE.

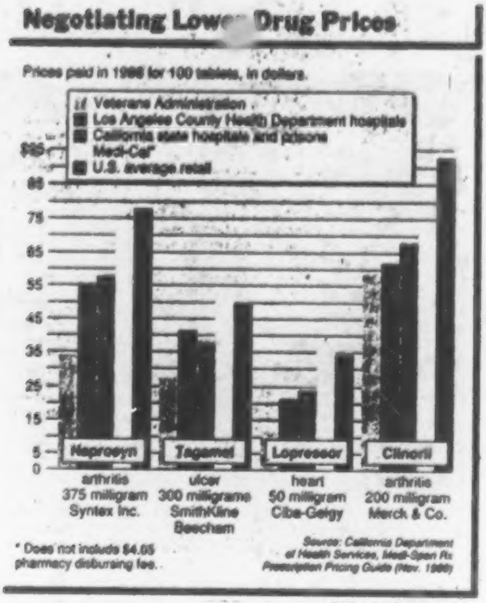
AS AN ARTICLE WHICH APPEARED IN TUESDAY'S NEW YORK TIMES BUSINESS SECTION SUGGESTS, THE TOLERANCE OF PRIVATE AND PUBLIC PRESCRIPTION DRUG BUYERS OF RISING DRUG COSTS IS WANING. THE WAVE OF THE FUTURE IS NEGOTIATED DRUG PRICES BETWEEN STATE AND PRIVATE HEALTH PLANS AND DRUG MANUFACTURERS. I WOULD ASK, MR. CHAIRMAN, THAT THIS ARTICLE ALSO BE INCLUDED IN THE RECORD.

MR. CHAIRMAN, WE HAVE THE OPPORTUNITY THIS MORNING TO DEMONSTRATE LEADERSHIP ON THIS ISSUE AND TO EXPLORE SOME OF THE OPTIONS AVAILABLE TO STATE MEDICAID PROGRAMS TO GET A BETTER DEAL FOR PRESCRIPTION DRUGS. I BELIEVE THAT THE PUBLIC SECTOR HAS MUCH TO LEARN FROM THE STRATEGIES EMPLOYED BY HEALTH MAINTENANCE ORGANIZATIONS (HMOs), HOSPITALS AND BUYING GROUPS TO IMPROVE THEIR NEGOTIATING POSTURE AND TO WORK WITH DRUG MANUFACTURERS TO REDUCE PRICES.

WHILE I REGRET THAT I WILL BE UNABLE TO STAY FOR THE DURATION OF THE HEARING, DUE TO OTHER COMMITTEE COMMITTMENTS, I LOOK FORWARD TO REVIEWING THE HEARING RECORD. THANK YOU, MR. CHAIRMAN.

NYT 11/14/89

Negotiating Lower Drug Prices



* Does not include $4.05 pharmacy disbursing fee.

Source: California Department of Health Services, Medi-Span Rx Prescription Pricing Guide (Nov. 1988)

The New York Times/Nov. 14, 1989

Price Revolt Spreading On Prescription Drugs

By MILT FREUDENHEIM

Beginning a buyer's revolt against sharply rising prescription drug prices, a growing number of state government and employer health plans are trying to force pharmaceutical companies to trim prices on brand-name products.

To back up their demands for discounts and rebates, the state and private health plans are threatening to drop some products from their lists of drugs approved for reimbursement.

The lists already favor low-priced generic versions of drugs that have lost patent protection. But now the health plans are demanding bids from makers of competing brand-name drugs that have no generic equivalents. Some health plans are even talking of boycotting some products of companies that refuse to cooperate.

A Price Surge Since '80

"We want to send a signal out to the physician, the pharmacy and the manufacturer that there has to be an end to tolerance of rising costs," said Dan Heslin, director of employee benefits at Rockwell International, an aerospace company that is negotiating with drug makers on prices and is even opening its own pharmacies to buy drugs in bulk at lower prices.

The price of drugs has risen 88 percent since 1980, "and it continues to go upward," said Senator David Pryor, Democrat of Arkansas, chairman of the Senate Aging Committee, which plans hearings on prescription drug prices for Thursday.

The Labor Department said prescription drug prices rose 9.2 percent in September from the month a year earlier, more than double the Consumer Price Index. Americans will spend $40 billion on drugs and related products this year, according to Federal statisticians.

The drug companies have been fighting the price demands. In California and Kansas, for example, they have been lobbying for legislation that would prohibit state Medicaid programs from excluding higher-priced products, arguing that such policies amount to second-class medical treatment for the poor. And while some pharmaceutical companies have agreed to discuss prices with some large employers and insurers, the purchasers say the companies have refused to give discounts and rebates on brand-name products, except to hospitals and large health maintenance organizations.

> 'There has to be an end to tolerance of rising costs.'

Hospitals and some H.M.O.'s have secured price concessions because they shortened the lists of drugs their physicians prescribe, putting pressure on the manufacturers to make deals. But patients not in H.M.O.'s who are covered by employers and Medicaid buy their drugs at thousands of pharmacies that do not have

Continued on Page D6

Price Revolt Spreads on Prescription Drugs

Continued From First Business Page

unified buying power. (The Medicare program for the elderly and disabled does not cover prescription drugs outside the hospital, and an expansion of the program to cover such expenses is virtually dead in Congress.)

In the political battling over drug prices, the health plans leading the revolt are supported by advocates for the elderly, who use more than 30 percent of all prescription products, and for people with AIDS.

They cite as examples the $6,500 annual cost of AZT, the only federally approved AIDS drug; $6,240 a year for erythropoietin, for anemia associated with kidney dialysis, and $1,375 a year for Eldepryl, a promising new drug for Parkinson's disease.

"Seventy percent of elderly Americans have no insurance for prescription drugs," Senator Pryor said.

'A Collision Course'

John Rother, legislative director in Washington for the American Association of Retired Persons, an advocacy group, said: "Drug prices are on a collision course with the political interests of business, older people and government." John R. McHugh, president of the group's mail-order drug service, said, "The brand-name manufacturers' prices in the last few years have been unconscionable."

Representatives of the Pharmaceutical Manufacturers Association, an industry trade group, said prices were rising because the revenues had to finance large research and development programs. They said the companies spent $6.5 billion on research, or 16.3 percent of their $46.2 billion in worldwide sales last year. "Costs of labor, materials, taxes and promotion have also increased in recent years," said Gerald J. Mossinghoff, the association president.

He said drugs, including those for ulcers and high blood pressure, had yielded enormous savings in overall spending on hospital care.

Securities analysts said drug makers have often raised prices to increas[illegible] even though sales as measured in units have been stagnant over all — about 1.5 billion prescriptions a year since 1982.

21% Increases in '89

The Upjohn Company, for example, has raised the price of both Xanax, a tranquilizer, and Halcion, a sedative, by 21 percent since January, as the number of prescriptions written for both products was dropping, said Ronald Nordmann, an analyst at Paine Webber Securities.

Because benzodiazepines like Xanax and Halcion can be addictive and their effects are often compounded by alcohol, physicians have begun to limit prescriptions for both drugs. New York State [illegible] the [illegible] and frequency of benzodiazepine prescriptions. And a Food and Drug Administration advisory committee recently recommended that Upjohn be required to warn that travelers who use Halcion may have memory lapses.

The New York Times/Paul Jen[illegible]

To fight rising prescription drug costs, Rockwell International operates a pharmacy for employees at one plant, where Michele Hartzler and other pharmacists dispense drugs that the company buys in bulk at lower prices.

The drug makers say drugs often have only a few years of strong earnings before losing ground to new products and, after their patent protection runs out, to low-priced generic versions. Robert H. Uhl Jr., an analyst at Salomon Brothers, said that by 1993 two dozen drugs with a combined total of $5 billion in annual sales will have lost patent protection.

Industry Highly Profitable

But pharmaceuticals are one of the country's most profitable manufacturing industries: Pretax profits were 22.6 percent of sales in the first half of 1989, compared with 7.8 percent for all manufacturing, the Commerce Department said. By another measure, pretax earnings amounted to 42.7 percent of shareholders' equity, compared with 21.5 percent for all manufacturing.

Rising costs for drugs are a major concern for large employers like the General Motors Corporation, which says it will spend more than $300 million this year for drugs for active and retired employees, up more than 20 percent from 1988.

"A lot of that comes right off the bottom line of their earnings report," said Mason Irving, a health-care expert at Arthur D. Little, a consulting firm in Cambridge, Mass.

The Big Three auto makers' major health plan, the Blue Cross and Blue Shield Association of Michigan, has obtained price rebates from drug manufacturers for its health maintenance organizations, said Thomas A. Needham, a senior pharmaceutical consultant with Michigan Blue Cross. "We may try to expand the rebates to all our business," he said.

Prices Compared

H.M.O.'s, which are prepaid health plans, and hospitals draw up lists of approved drugs, known as formularies, in consultation with doctors and pharmacists. When there is a choice of products deemed equally safe and effective, price becomes an important consideration.

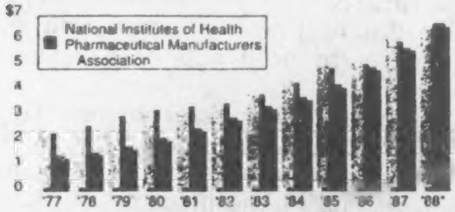
"We negotiate with manufacturers and all vendors," said John Middleton, president of Diversified Pharmaceutical Services, a unit of United Healthcare Inc., an 800,000-member H.M.O. based in Minneapolis.

Rockwell, which has 110,000 employees, operates its own pharmacy at a plant in Iowa and is planning to open pharmacies for its employees in Texas and California. Mr. Heslin said manufacturers had offered to supply drugs to Rockwell employees by mail at special prices.

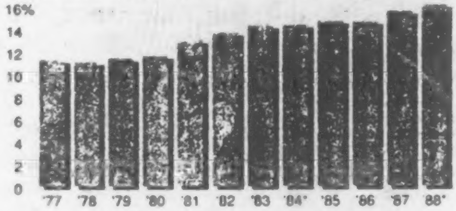
Five Los Angeles-area aerospace companies — Rockwell, Lockheed, Hughes Aircraft, TRW and Northrop — have commissioned a study of "the cost-effectiveness of direct pharmacy contracting," said Michael J.

One Factor in Rising Drug Costs

Research Expenditures Are Climbing . . .
Expenditures by members of the National Institutes of Health and Pharmaceutical Manufacturers Association, in billions of dollars



. . . And Are a Growing Percentage of Sales
Research expenditures by the members of the Pharmaceutical Manufacturers Association, as a percent of U.S. sales. and exports.



* Estimate

Sources: National Institutes of Health, Pharmaceutical Manufacturers Association

Some health plans are considering boycotts.

Barbert, a principal with Mercer Meidinger Hansen, a benefits consulting firm. "The drug manufacturers are truly an oligopoly," he said. "But employers are getting closer to the door to influencing drug prices."

Stephen Schondelmeyer, director of the Pharmaceutical Economic Research Center at Purdue University, said: "In many cases, the purchasers of health care are now as large as the pharmaceutical manufacturers. We're seeing a leveling out of market power between purchasers and producers."

Deere & Company, a farm machinery manufacturer, operates its own health maintenance organization with 175,000 members. "Both brand-name and generic drug manufacturers have expressed an interest in talking to us," said Richard J. Van Bell, Deere's personnel and health care operations director.

Bids Sought

Officials of Medicaid are also pressing for rebates in at least 14 states. Medicaid will spend $3.3 billion on prescription drugs in 1989.

The manufacturers have rebuffed the states in most cases, but last year, when Kansas called for competitive bids on 30 drugs, "several companies, including brand-name manufacturers, responded," said John W. Alquest, the state's Medicaid commissioner. Bids were accepted on six products, each a lower-priced generic version of a brand-name drug. "If a doctor prescribes the brand-name, we just won't pay for it," he said.

Mr. Alquest said drug manufacturers had tried without success to persuade the Kansas Legislature to prohibit the bidding program.

Last month, the California Legislature authorized the state's Medi-Cal program for low-income patients to add or delete drugs from its approved list, thus strengthening the state's bargaining power. Norman Hartman, a Medi-Cal spokesman, said the manufacturers had rebuffed earlier requests to negotiate, and had "dumped a ton of money trying to defeat the law."

Medi-Cal has been paying $54.90 for 300 milligrams of the anti-ulcer drug Tagamet, made by SmithKline Beecham, said Richard Iniguez, a Medi-Cal section chief. But because of negotiated discounts, he said, California hospitals and prisons paid $38.50 for the same amount, Los Angeles County Health Department hospitals paid $41.54 and the Veterans Administration paid only $27.60.

Employers, insurers and pharmaceutical industry experts said concerns about drug prices have been compounded by recent Congressional votes to cut back the Medicare program for catastrophic illness, which would have paid for some prescription drugs for elderly Americans. But Senator Jay Rockefeller, who heads a bipartisan Senate-House commission on health care, said a bill to revive a drug benefit would probably be introduced next year.

Senator **Heinz**. I would like to ask Mr. Green a question. Taking a slightly different angle than just the cost angle of the drugs, Mr. Green, your story is a struggle against the odds to remain independent and you are very nervous about what is going to happen to you in the future.

I would like to know whether you have any insurance, other than Medicare, to help you defray the cost of your prescription drugs.

Mr. **Green**. If I may refer to one thing, also, concerning your question, you were talking about the prices of Mestinon. I get mine through the Myasthenia Gravis Association, which is one of the best organizations in the country. Without them, I would be really suffering if I could not get my drug through their pill bank. They have really helped me.

As you asked about the insurance, they said I could get it free, but they said I would have to sign a paper that I am in very deep poverty and cannot afford to buy the pill, and also that I don't have any insurance.

I do carry Blue Cross, which pays for $500 of medicine a year. But the first $100, $400 to $500, you pay yourself. But the premium I pay is $70.80 per month. You can get a premium without the coverage for medicine for $40. So in other words, you are paying around $28 or $29 a month for your own medicine.

When you get through at the end of the year, with the price of $87 a month for your medicine—I didn't figure it out exactly—they are paying around $125 or $130 for your medicine, you are paying for it yourself. So you are not actually benefiting.

Senator **Heinz**. So the insurance concept of protections in this case does not work. You are not getting any benefits.

Mr. **Green**. It does not. If the medicine keeps on going up, you're in a deeper hole than you were before.

Senator **Heinz**. Mr. Chairman, that's my point. Most of the elderly have Medigap policies, as I understand it, or private insurance of one kind or another, that purport to provide some kind of insurance on prescription drugs.

A lot of them, and Mr. Green's is one example, simply do not. It seems to me that if we are going to have meaningful Medigap insurance, it ought to make the hole in coverage smaller, not keep it as large, or in some cases, make it larger. That is Medicavern, not Medigap. I know that is not a specific subject of this hearing, but it is a subject we should look at, maybe on another occasion, or at least in the Finance Committee, where a number of us serve.

Mr. Green, I thank you very much. I do have other questions, but don't want to go beyond my time.

I do want to ask Mr. Hodel one question. Mr. Hodel, you discussed the fact that social workers sometimes encourage people to quit their jobs in order to qualify for Medicaid.

Mr. **Hodel**. That is certainly correct.

Senator **Heinz**. Do you know whether that is also true for people who are HIV positive and/or persons who have AIDS?

Mr. **Hodel**. Generally, with people who are simply HIV positive, many of those people are not yet ill. While they begin to incur medical expenses, they do not become extraordinarily high until they do become ill.

It is generally assumed among social workers that once one begins to develop serious symptoms, that it is a matter of decline after that. It is generally assumed that one will quit one's job at some point.

Many people with AIDS, because they are in their thirties or forties, are without savings that will carry them for very long, and so it is assumed that they will eventually end up on Medicaid.

Senator **Heinz**. To the extent that they are advised to quit their jobs and go on Medicaid, is that in substantial part because of the cost of drugs like pentamidine?

Mr. **Hodel**. Certainly. For people without insurance, medication costs for AIDS can amount to thousands and thousands of dollars per year. I personally know several people who pay well over $1,000 per month for medications, and I should point out that that includes people who do not take AZT, which is perhaps the most expensive.

Senator **Heinz**. But one of the reasons they do go on Medicaid and quit their jobs to go on Medicaid is because of the cost of drugs?

Mr. **Hodel**. Absolutely. Because Medicaid will cover the costs of those drugs.

Senator **Heinz**. Mr. Chairman, my time is up. I must observe that a policy that encourages people to stop work so they can continue to function is an upside down policy.

Mr. **Hodel**. It would seem so.

Mr. **Pryor**. Thank you, Senator Heinz.

Senator Reid.

Senator **Reid**. I have no questions at this time.

The **Chairman**. All right. I believe Senator Cohen was next and then Senator Bradley.

Senator **Cohen**. Mr. Green, you mentioned the Myasthenia Gravis Association of Western Pennsylvania. Do they provide different types of medications at a lower cost to you and others who are afflicted with this disease.

Mr. **Green**. The medication they provide for me is Mestinon. It is provided at quite a bit lower cost than what I can buy it for at the drug store.

Senator **Cohen**. According to your statement, once Hoffman-LaRoche transferred the distribution rights to ICN Pharmaceuticals, they no longer sold at either a wholesale or reduced rate to the Association of Pennsylvania. Is that correct?

Mr. **Green**. According to statement, when I was notified from the pill bank in Western Pennsylvania that the distribution rights had been sold to ICN, I called up the branch in Chicago. They told me it was going up to $87 because they had refused to honor the contract in Western Pennsylvania and elsewhere that was for $40. In other words, the contract had expired as of June 1, or whatever it was, and that was it. After that contract expired, ICN refused to extend the contract at that price.

I think the representatives of the Myasthenia Gravis Association could give you a better idea as to who did what, but the price did go up to $87. But the Myasthenia Gravis Association in Chicago got that for me. I get the pills out of what they call the American Drug

RX, out of Salt Lake City, UT. The medicine is sold to them, and worked through the pill bank at that price.

Otherwise, today, in our town it is $136 per 500 pills. I heard last night that in New York City and some places, it was $150 to $160 for 500 pills, and that the price is going up again. So where it stops, nobody knows.

Senator **Cohen**. The association that you are getting the pills from now charges you how much, $87 and it is going up to $93?

Mr. **Green**. It has gone up 8 percent, yes, just the other day when I was preparing this speech, on November 1.

Senator **Cohen**. And that's still at a discount rate?

Mr. **Green**. That is a discount rate, but the Myasthenia Gravis Association, according to what I understand, they are absorbing a lot of the cost.

Senator **Cohen**. In other words, if you did not have access to this association, the cost to you would be much higher even than $93?

Mr. **Green**. Oh, yes. I was very fortunate in one respect. I heard of this organization through Muscular Dystrophy, they told me about this organization in Pennsylvania. When I wrote to them and explained my situation, they told me it would cost $10 to join the organization, a final membership fee. Since then I have been very fortunate that I can get the pills from them. The way the cost goes up and up, we never know what it is going to be.

Senator **Cohen**. How many people have this disease that do not have access to the organization?

Mr **Green**. There is an estimated 125,000 to 150,000. I might be a little lower or higher. The thing is, if I may point out, I stated in my speech that it is a rare disease at that point. A lot of people have Myasthenia Gravis but they don't know it. It took around 3 or 4 weeks of testing to finally figure out that I have it. After all kinds of blood tests, they finally determined that's what it was.

Today, a lot of people have it but they still don't know what it is. The think it's just a muscle deficiency, or arthritis, or something like.

Senator **Cohen**. And if they do find out what they have, they cannot afford to take care of it?

Mr **Green**. When it gets to that point, they estimate it will get higher and higher, your medication remains the same, there is no generic drug, either you pay for it or take the consequences. You have to take it to live. It controls the disease, but there is no cure for it.

Senator **Cohen**. Thank you.

The **Chairman**. Mr. Hodel, the charts that you brought before the committee today in your statement indicate that since 1984, there has been a 400-percent increase in the price of this particular drug that is life-sustaining to many members of the AIDS community.

Have you, or anyone else who might be a spokesman for the community gone to this particular company, Lyphomed and attempted to find out, one, why this price is justified, or two, if they are going to deem that they do or do not have a social responsibility in this field? Has there been any contact with the company?

Mr. **Hodel**. There have been numerous attempts by AIDS advocates and by the media to learn from Lyphomed the justification for the price increase. Most of those attempts have been unsuccessful. There has also been a concerted effort among 20 of the largest AIDS organizations in the country to contact Lyphomed to request a meeting concerning pentamidine pricing. As of 2 days ago, Lyphomed has indicated that they would meet.

The **Chairman**. That they would meet?

Mr. **Hodel**. Yes. That was news I received just Monday of this week. That meeting has not yet taken place.

The **Chairman**. I will say this, and I probably shouldn't, but some of the companies, the manufacturers, have expressed an interest in meeting with some of the members of this committee. I know my friend Senator Warner and Senator Heinz and others have thought it might be constructive to sit down with the manufacturers and talk about this. Maybe that would be constructive.

I have reservations about this because I think that these drug pricing mechanisms should be in the public, not the private, domain. I truly feel that as the Government is probably the No. 1 purchaser of many of the drugs we are talking about we should have public access to the reasons for these price increases.

The drug manufacturers may not know it, but they are digging themselves into a very deep hole. The Congress is not going to stand around and watch drug prices in the community that you represent go up 400 percent, 238 percent for Mr. Green's drugs. We're not going to stand here and watch people in Italy pay 41 cents for Mrs. Bivens' pill and $1 in Canada and $2.38 here.

This system is not going to permit that. What we do with this problem is another question, but there is no doubt that something is going to be done. This system is going to respond.

Senator Warner.

STATEMENT OF SENATOR JOHN WARNER

Senator **Warner**. Mr. Chairman, I would say that we ought to at least give the companies an opportunity. They have responded with a willingness to come forward and talk to members of this committee. They do operate in a free-enterprise system. It is the system which has produced these magnificent drugs. They have proprietary interests, and I, like you, want to get at the bottom of this issue. Indeed, all across America we should get at the bottom of this issue.

Nevertheless, we should do it in fairness and within the framework of the free-enterprise system which we have in this Nation.

The **Chairman**. I feel like, Senator Warner, if these manufacturers were sitting there in your office or mine, and we closed the door, and they told me some deep, dark secrets that inadvertently in a hearing like this, I might just blurt them out. I don't want to do that.

Senator **Warner**. We had better be prepared to take those risks if we are going to get at the bottom of these issues. These are important issues, and let's get on with it.

The **Chairman**. Senator Warner, do you have any questions for these witnesses?

Senator **Warner**. Not of this panel. I will wait for the next panel.

The CHAIRMAN. Senator Cohen or Senator Heinz.

Senator HEINZ. No further questions.

The CHAIRMAN. I have one question for Mr. Green. You had an opportunity there a year or so ago, or months ago, when the prices of these drugs started going up dramatically, to sign a statement that you did not have the ability to pay for these drugs any longer. You would basically have become a Medicaid recipient. You could have signed a letter of impoverishment. I think you had that opportunity. You refused to do so. Is that correct?

Mr. GREEN. Yes, sir. I'm not in poverty, and I don't ask for charity. The thing that really bothers me and gets me, is that one company can control the price of one pill, Mestinon, which has been in existence for a long time. The product is the same, but they keep raising the price.

If you have to have that to control the disease, it's the most effective drug I can take, it controls what I have, which is called ocular-neuromuscular disease. It started in my eyes. I am very fortunate in one respect. A lot of people have it in their chest, in their speech, and some people really have it bad.

So far, the drug has helped to control mine, and I need it. I cannot say "I need another pill." My doctor himself said, "Take the pills, I don't want to take you off them because I don't know what the side effects will be." So as long as I'm doing well with it, I am taking it. But why should a company take advantage of me? Not only me, but I am speaking for other people that take Mestinon.

The CHAIRMAN. If we become angry—let's say that Coca-Cola has raised their prices too much, then we have an option. We can drink Pepsi-Cola. You don't have an option like that here. We are dealing with a pretty monopolistic environment, where there are no options for the consumer, and very few options for the Government. But we are going to talk about some of the options for the Government in our next panel.

Does anybody have any follow-on questions or statements?

Senator Heinz.

Senator HEINZ. Just a comment on the discussion you and Senator Warner were having a moment ago on the drug companies. I think we need to find a way to talk with the drug companies. But we need to understand that there are sensitive proprietary issues involved. I am hopeful that through meetings, we can understand these proprietary concerns, and decide to what extent they are legitimate concerns.

The present situation is kind of a standoff, with concerned members unable to talk to them and they, unwilling to talk to us. That's clearly unacceptable to all involved. Nonetheless, because it is unacceptable is not to say that they may not have some legitimate concerns.

So I hope, Mr. Chairman, that we can find a way to have a dialog. I support you in that goal.

Senator WARNER. One thing, Senator Heinz. I think you said they are unwilling to come forward. It's my understanding that they are willing, providing that we can give adequate protection to the laws of this land which provide for proprietary interests.

Senator HEINZ. I think it is a semantic issue.

Senator **Warner**. I know, but I don't want people to leave thinking they are unwilling.

Senator **Heinz**. The unwillingness is that they don't want to come up here without our having a clear understanding of what their proprietary concerns are. I was not using the term in a pejorative sense, I was using it, I thought, descriptively. I think probably now that we understand the semantics, we agree.

Senator **Warner**. We do. Because I have made an effort to get out and talk with them, and gain this information. I have had them, individually and collectively, express to me a willingness to come in and talk providing we accord them certain rights. If we are to get to the bottom of this issue, we have got to figure out how to solve that problem of receiving that evidence.

The **Chairman**. I thank my colleagues very much. We are going to dismiss this panel and call our next panel. We thank all of you very, very much. This has been very constructive testimony. Thank you.

Ladies and gentlemen, our last panel related to the victims of high prescription drug prices. The second panel will describe what the private sector and the State of Virginia are doing—or trying to do—to get a better and fairer deal on the price of prescription drugs.

We have three witnesses. In just a moment I am going to allow Senator Warner to introduce his constituent from South Hill, VA, Mr. Mike Berryman, who is chairman of the board of Medical Assistance Services. We also have Mr. Tery Baskin, the director and chairman of PACE Alliance, in Little Rock, AR, and Dr. Norrie Wilkins, vice president of pharmaceutical management, accompanied by Dr. Donna Schmidt, manager for clinical pharmacy programs, Partners National Health Plans, of Minneapolis, MN.

We are very grateful for the presence of the three of you. Let me yield at this time to my good friend, Senator Warner from Virginia.

Senator **Warner**. Thank you, Mr. Chairman. We welcome the panel, particularly the distinguished Virginian, Mike Berryman. Mike if I may say, you represent the all-American pharmacist. You are out there fighting. You are out there trying to achieve the results that this committee is striving to achieve.

The difference is that you have had some success, and you have negotiated on behalf of your group in Virginia with the pharmaceutical associations, and you have been able to produce results for those who come into your store every day, to get your advice and your assistance, your compassion and understanding.

Good luck.

The **Chairman**. Thank you. Mr. Berryman, as a personal note, about once a year, and only once a year, your distinguished Senator and friend, Senator Warner, takes off a little time from his Senatorial responsibilities to play golf. About 3 weekends ago, I shared the rare opportunity of playing golf with Senator Warner. I might tell you that his drive on the first tee, we measured it, was 283 yards. I won't tell you in which direction it was.

Senator **Warner**. I tell you, I took an aspirin that night after I was finished.

The CHAIRMAN. We will hear from Mr. Berryman first, I think, and once again, the basic thrust of this panel is how we might get drug manufacturers to the bargaining table, what is happening out in the private sector and the States and how we can negotiate a fairer deal for the American consumer and taxpayer.

Mr. Berryman.

STATEMENT OF R. MICHAEL BERRYMAN, CHAIRMAN OF THE BOARD OF MEDICAL ASSISTANCE SERVICES, SOUTH HILL, VA

Mr. BERRYMAN. Thank you, Senator Pryor, and members of the committee.

The CHAIRMAN. Can I ask you this? Can each of you perhaps hold your statement to 5 minutes each? Then we will have questions, because I think other Senators are coming. I think there also will be a vote on the Senate floor before too long, and I hate to have you just sitting here. So if we could proceed under the 5-minute rule, we will put the full body of your statements into the record.

Mr. BERRYMAN. I am Mike Berryman, and I have been a practicing pharmacist for 25 years in Kenbridge, VA, and South Hill. I am also the current chairman of the board of Medical Assistance Services, which oversees Virginia's Medicaid program. From 1984 to 1985 I was president of the State pharmaceutical association. I also sit on the Virginia Joint Subcommittee on Health Care for All Virginians, which is wrestling with the growing problem of providing affordable health care to 880,000 citizens in Virginia that have no insurance.

I appreciate the opportunity to share my views with you today on discriminatory pricing in the prescription drug industry, and the ever-increasing costs in that industry. The Commonwealth is very concerned with the increasing costs of prescription drugs, particularly in its Medicaid program. Something is seriously wrong when an incredible disparity in the cost of drugs is realized.

For example, the Medical College of Virginia, which is located within six blocks of the Medicaid office, and the Medical College is a State agency, of course, purchases transdermal nitroglycerin patches for a penny for a box of 100 patches, while the Department of Medical Assistance Services, a sister State agency, must pay in excess of $1 per patch for the same product.

Unfortunately, this example is completely indicative of the discriminatory pricing strategies that drug manufacturers pursue in their quest for unconscionable profits.

Another example of which I am personally aware involved an elderly lady who lived in my community on a fixed income of $168 a month. She requires several medications per month, which she purchases at our pharmacy at a cost of $120. Yet, if she could purchase those same drugs at discriminatory preferential prices, she would spend only about $30 per month. I submit to you that something is wrong.

I have been asked specifically within the context of Virginia's Medicaid program, why Virginia is searching for ways to reduce the costs of prescription drugs, given the fact that drugs are a relatively modest percentage of Virginia's Medicaid budget. They do represent only 7 to 8 percent of the budget, nevertheless, it is a $67 million cost.

In Virginia, we have had some very traumatic issues that we have had to confront in the past year. One had to do with the transplant issue. We had to vote to deny transplant coverage for liver and bone marrow transplants because of a lack of funding in the State.

So if we can save money on the drug program, and reduce some of the money that we are spending in that effort, we will be able to expand our services to other recipients.

To that end, Virginia has imposed restrictions on the use of new drug products that are not necessarily of any new therapeutic value. Virginia has eliminated coverage for nitroglycerin patches because their cost cannot be justified when cheaper and equally efficacious drugs are available.

In addition to these steps, Virginia's General Assembly has established a legislative study commission to study the issue of Medicaid reimbursement of drugs. That committee is seriously considering two options. One, a rebate program, and two, a restricted drug formulary.

If enacted, these initiatives should put the drug manufacturers on notice that Government cannot continue to tolerate the rapid and unreasonable escalation of drug costs. If these do not work, then perhaps, as you have suggested, Senator Pryor, it is time for the Congress to take steps to control the unreasonable pricing policies of prescription drug manufacturers.

I want to add that we in Virginia, and I know your committee as well, want a viable, healthy drug industry in this Nation. They have made significant contributions to society, and we need that. We also need the industry to come to the table.

All providers in the Medicaid program, hospitals, physicians, pharmacists, everybody, has shared the cost burden and many provide services at cost or below, or just a smidgen above. Today, our problem in Virginia is that we have been unable to get the manufacturers to share any of that burden. They will talk to us, but we don't seem to get any substantive results.

It appears that the Congress and Medicaid agencies need a joint effort to try to bring these costs in line, at least for agencies like Medicaid and Medicare.

I appreciate the opportunity to be here today, and I would be very happy to answer any questions you have.

[The prepared statement of Mr. Berryman follows:]

ADDITIONAL STATEMENT OF MR. R. MICHAEL BERRYMAN
to the Senate Special Committee
on Aging Concerning Prescription Drug
Manufacturer Pricing Policies and Practices
November 16, 1989

Mr. Chairman and Members of the Committee, I am Michael Berryman, a practicing pharmacist in the Commonwealth of Virginia. I am also the Chairman of the Virginia Board of Medical Assistance Services, which oversees the Virginia Department of Medical Assistance Services, Virginia's Medicaid agency. I am a past president of the Virginia Pharmaceutical Association, and I also sit as a member of the Joint Subcommittee on Health Care for All Virginians, which is dealing with how to finance health care for the indigent and the uninsured.

Virginia elected to participate in Medicaid in 1969. Since that time, the Medicaid budget of the Commonwealth of Virginia has grown from fifty-five million dollars per biennium to almost two billion dollars per biennium today. Remarkably, a substantial portion of this growth in the Medicaid budget has occurred between 1985 and 1989. In that time frame, the Medicaid budget expanded by 103%. I am sure that it comes as no surprise to any of you that Virginia, like every other state, is facing a fiscal crisis insofar as controlling increasing health care costs, financing those increased costs, and insuring the delivery of needed medical care services to the entire population, but particularly to those individuals who are indigent.

Cost containment in Virginia's Medicaid program has been an ongoing concern since at least 1975 when the Commonwealth first felt the need to constrain a budget that appeared to grow without any control whatsoever. The 1975 cost containment efforts were directed primarily at the hospital industry.

Between 1975 and 1982, there were other minor cost containment efforts but they were principally technical in nature. It was not until 1982 when the Commonwealth, again, pursued significant cost containment efforts. At that time, the Administration was so concerned about the Medicaid budget that it gave serious consideration to eliminating coverage for the medically needy in Virginia which, as you know, is an optional coverage group for Medicaid.

Since 1982, every session of the General Assembly has wrestled with the problem of containing cost in Medicaid. As a result, Virginia has examined and re-examined and examined again every conceivable aspect of the Virginia Medicaid program to identify areas in which cost savings can be effected. Pharmacy costs are no exception.

Virginia was one of the first states to develop an effective means for providing and reimbursing prescription drug costs in a Medicaid program. Virginia elected to provide prescription drugs as part of its program, even though it was an optional service, because of its belief that the availability of drugs would prevent more serious illnesses, requiring expensive hospitalizations. Simply put, prescription drugs can and do contain Medicaid costs because they are essential to preventive medicine. Accordingly, Virginia is a strong supporter of an effective pharmacy program in state Medicaid programs. Prescription drugs are "cost-necessary."

Nonetheless, Virginia's program could not ignore the fact that the pharmacy budget increased 71% from 1984 to 1988. That increase was attributable to the increased costs of the drug products themselves, principally sole source drugs where prescription drug manufacturers enjoy carte blanche in setting prices. Accordingly, in 1988, the General Assembly directed the program to reduce pharmacy expenditures by $5.5 million and gave the Department the responsibility of identifying the means for achieving such a reduction. After several months of working with the Virginia Pharmaceutical Association, the Virginia Association of Chain Drug Stores, and the Pharmaceutical Manufacturers Association, the 1989 session of the General Assembly put in place four cost containment measures for pharmacy. Those cost containment measures were as follows: (1) one professional dispensing fee per drug per month; (2) an increased recipient co-pay; (3) discontinuance of coverage of transdermal delivery systems; and (4) limitation on coverage of new drug products. In addition, the General Assembly passed House Joint Resolution No. 403, which authorized a legislative subcommittee to study the issue of rising pharmacy costs in particular. Accordingly, the General Assembly recognized that pharmacy costs were sufficiently unique and important to require its own, separate study.

The HJR No. 403 Subcommittee has been meeting throughout the past several months, acquiring information and trying to identify appropriate solutions for cost containment in the Medicaid pharmacy budget. Although Medicaid pharmacy costs are only 7-8% of the total Virginia Medicaid budget, the Commonwealth is concerned that that part of its budget is growing without reason; normal inflationary factors are not the source of the pharmacy increases.

The Commonwealth will undoubtedly consider a number of options for trying to reduce drug costs. First, the Commonwealth is looking seriously at the adoption of a restricted drug formulary for use in the Medicaid program. The Virginia Pharmaceutical Association and the Virginia Association of Chain Drug Stores actively support this alternative. The Pharmaceutical Manufacturers Association, on the other hand, opposes the adoption of such a formulary and, indeed, that organization has even advocated the elimination of the restriction on new drug products, which the 1989 General Assembly mandated.

Secondly, the Commonwealth has discussed the option of some form of rebate program or a most-favored nations program whereby each drug manufacturer, depending on the volume of its drugs dispensed to Medicaid recipients, would rebate a particular amount of money to the Department of Medical Assistance Services. When this possibility was specifically discussed with the Pharmaceutical Manufacturers Association by Virginia's Medicaid Director, he was quickly reminded by PMA that he had no legal authority and that that was not an option PMA would support. The underlying theory for such a rebate program is the fact that other agencies of the Commonwealth which directly purchase pharmaceutical products, such as the Medical College of Virginia and the various health agencies in Virginia, are able to obtain those drug products at costs that are significantly below the cost that retail drug stores are able to acquire them. For example, it has been reported that the Medical College of Virginia is able to buy a box of transdermal nitroglycerin patches at a price of a penny for 100 patches, whereas, the Department of Medical Assistance Services must pay in excess of $1.00 per patch. It makes little sense for a welfare program to pay premium prices for drug products when sister agencies may purchase those same products at a greatly reduced cost.

Thirdly, the Commonwealth will also pursue a reinvigorated and more thorough drug utilization review program to ensure that physicians and Medicaid recipients are using drugs under appropriate conditions of medical necessity, as well as ensuring efficiencies and economy.

Obviously, the real difficulty in attempting, within the context of a Medicaid program, to control the rising costs of drugs is the fact that the Commonwealth does not have a Medicaid provider contract with any drug manufacturer. Instead, the Commonwealth has a contract only with the retail pharmacy. Accordingly, to effect a rebate program or a most-favored nation clause raises some serious legal questions as to the authority of the state to enact cost containment measures that directly affect the drug manufacturers. Accordingly, to the extent that this Committee may be considering amendments to federal law, I certainly hope that it will give very serious consideration to mechanisms that will allow either the Federal Government or individual state governments to impose appropriate cost containment measures upon drug manufacturers. The Congress must appreciate that for the past 30 years it has effectively set health care policy. Therefore, Congress should act to establish a clear legal basis for cost containment measures in which drug manufacturers participate.

Your staff also asked me to address briefly whether the states ought to be allowed to negotiate lower prescription drug prices with some kind of rebate program such as I have discussed. Obviously, I believe that is a viable alternative, and one which would be made more legally defensible if the Congress took appropriate legislative action. Nevertheless, I point out to the Committee that, if such authority is not provided the states, then the only other realistic possibility for addressing this problem is to impose a system upon the drug manufacturers which restricts them in setting their own pricing policies. Obviously, this is an extreme alternative, but, if drug manufacturers are not going to be reasonable in their charges, then government must act. I appreciate the opportunity to address the Committee today Mr. Chairman, and would be more than happy to answer any questions the Committee may have concerning the situation in Virginia. In the event that I do not have specific facts and figures that may be of interest to the Committee, I shall make every attempt to provide them to the Committee at some later time.

The CHAIRMAN. We are very grateful for your statement this morning. I am sure we will have a question or two momentarily.

We now have Tery Baskin, from Little Rock. Tery, we welcome you today. You operate a multi-State buying group called PACE Alliance, an organization that buys drugs less expensively and passes those savings on to the general public.

Tery, we would like to hear your statement today.

STATEMENT OF TERY BASKIN, DIRECTOR, CHAIRMAN, PACE ALLIANCE, LITTLE ROCK, AR

Mr. BASKIN. Thank you, Mr. Chairman and members of the committee. I appreciate the opportunity to come before you today, and make these comments.

My name is Tery Baskin, I am a practicing pharmacist. I have been a pharmacist for about 12 years. I was also president of our State pharmacy association in 1985 and 1986.

This morning, I would like to address three areas. I would like to talk to you about a workable chargeback system for prescription drugs, I would like to discuss the feasibility of a State Medicaid program using a chargeback system, and also to talk about the use of a formulary to be used in order to lower costs by obtaining bid prices on brand name prescription drugs.

The PACE Alliance is a retail pharmacy buying group which contracts with companies in order to achieve lower prices for goods and services used by pharmacies. The buying group currently has about 1,600 drug products on bid. We use a system or series of prime vendor wholesalers to distribute all of our contract items to member pharmacies.

We employ a chargeback system to ensure that only members of the PACE Alliance can purchase our contract items at the bid prices. Our prime vendor wholesalers pay their regular price for a product, and if they sell one of these products to a member of our group, they bill the pharmacy, get the contract price, then charge the manufacturer the difference.

The PACE Alliance supplies the manufacturer with a list of members, so that when they receive a chargeback from the wholesaler, they will know the item was sold to a member of our group.

PACE has been using this chargeback system for the past 4 years. Many hospital buying groups have saved millions of dollars by employing this system for many years. I believe this system would work very well for State Medicaid programs in reducing the cost of brand-name prescription drugs.

I think it would be a very simple system to employ. There are three necessary steps. First of all, the State would have to award a contract to a particular company for a certain prescription drug. Second, the pharmacy would pay their regular price for the drug, dispense the drug to a Medicaid recipient and then be paid their normal price by the State. Third, the State would then submit a chargeback to the manufacturer for however many units of that drug that had been dispensed, and there would be a chargeback based on whatever the bid price was.

This system has two benefits for the manufacturers. First of all, pharmaceutical companies are familiar with chargeback systems, because they currently use it for their contract sales. Second, the company would know—it would have an assurance—that the prescription had been dispensed to a Medicaid recipient, because they would only be billed for prescriptions for which the State had already paid the pharmacy.

In order for the State to be able to obtain bid prices on brand-name prescription drugs, there will need to be more than just large volume, there will also need to be a formulary in place. A formulary quite simply states which drugs will be paid for and which drugs will not be paid for.

The decisions regarding which drugs to place on the formulary needs to be made by a committee of physicians and pharmacists. Patient care must be uppermost in our minds, but enormous savings can be achieved without sacrificing any patient care at all.

Normally, obtaining contract prices is dependent upon volume, but that is not the case with prescription drugs. Let me give you an example of this point. PACE Alliance has over 2,200 pharmacies buying from our prime vendors. This represents better than one in every 30 pharmacies in the United States.

However, of our 1,600 pharmacy bid items, less than 10 percent of them are for brand-name prescription drugs. Even though we have been requesting bids from brand-name manufacturers for 4 years now, and we represent far more volume than many small HMO's and hospitals that have received bids and have contract prices.

The difference is that these entities all have a formulary which gives the manufacturer an economic incentive to bid, because if they don't, their products won't be sold or used for these patients.

The use of a formulary is not a new idea. It has been used for years by many hospitals, HMO's, the VA medical system, and even some State governments for their health departments and State hospitals.

In conclusion, let me state that in order for a State Medicaid program to be fiscally responsible with taxpayer dollars, they should be obtaining bid prices on brand-name drugs. Medicaid programs would not be creating new prices for these drugs, only asking for the best price that already exists in the marketplace.

Thank you very much.

The CHAIRMAN. Thank you very much, Tery.

Dr. Norrie Wilkins is from Minnesota. You are the chief pharmacist, I understand, Dr. Wilkins for a large Minnesota HMO called PARTNERS. You have developed some strategies for dealing with, and bringing the manufacturers to, the bargaining table.

You have also developed a formulary, I understand. I have it in my hand and was just thumbing through it to look at your particular formulary you have developed for use in that HMO.

We look forward to your statement.

STATEMENT OF DR. NORRIE WILKINS, VICE PRESIDENT OF PHARMACEUTICAL MANAGEMENT, PARTNERS NATIONAL HEALTH PLANS, MINNEAPOLIS, MN, ACCOMPANIED BY DR. DONNA SCHMIDT, MANAGER FOR CLINICAL PHARMACY PROGRAMS, PARTNERS NATIONAL HEALTH PLANS, MINNEAPOLIS, MN

Dr. **WILKINS.** Thank you, Mr. Chairman. Members of the Committee on Aging, both Dr. Schmidt and myself thank you very much for this opportunity to share with you the business model used by PARTNERS National Health Plans to manage pharmacy costs for managed care members.

The PARTNERS program has been both financially successful and instrumental in increasing the quality of drug prescribing for members by focusing management expertise on four critical factors.

The first is establishing cooperative relationships. Senator Pryor, I would recommend that you do pursue ongoing discussions with the pharmaceutical manufacturers.

Second, building a clinical management program that evaluates the cost and effectiveness of medications.

Third, we have built a volume pricing program which links clinical decisionmaking—and the comments by Mr. Baskin are certainly true here—we have linked clinical decisionmaking to the formulary process and price negotiations.

Fourth, we have built a better managed care model through research and development.

The mission of the PARTNERS pharmacy program is to be the industry leader in managed care pharmacy, providing quality drug therapy to our members while containing member clients' costs, and producing a profit for PARTNERS. PARTNERS in Pharmacy Management has identified key factors which have contributed to the escalating cost of pharmaceuticals.

The first is inflation. In our managed care system, we see drug inflation increasing 1 to 1½ percent each month. The second is new drug technology, new drugs in 1988 were 48.8 percent more than their replacement therapy.

The third is patient demand—we have seen advertising for new medications to our members which has increased the demand for expensive new products. In a managed care model, since most patients pay on a co-payment level, the members and the physician have been insulated from prescription prices.

The fourth reason is physician prescribing. The drug industry spends millions of dollars yearly to influence physician prescribing.

The business model that we adopted at PARTNERS is to control and manage the pharmacy benefit at those four key points. Pharmaceutical managed care systems must be able to control drug costs by establishing management programs that address each of those influencing points and associated costs. Therefore, the PARTNERS model was built to support and maintain strong, balanced relationships between the pharmaceutical manufacturers, the physician, the patient, and the pharmacist.

The success of this program is founded on the establishment of a clinical pharmacy program which is directed by Dr. Donna

Schmidt. The goal of the clinical services division of PARTNERS in Pharmacy Management is to provide a method for defining, assessing, and improving the efficacy, safety, and costs of drug usage in the members that we serve.

The objectives of the clinical staff are first of all to establish rational prescribing guidelines, to minimize needless expenditure of resources, to increase physician awareness of efficacy and safety, to serve as a research team to oversee and prevent prescribing problems, and to redefine and develop reporting systems.

The products of our clinical pharmacy division are first of all the formulary. The formulary is the list of drugs that we find to be reimbursable in our managed care model. As part of the formulary, we have what is called a drug update, which is a monthly newsletter to our physicians. That newsletter explains the policies and procedures of the formulary process. We have linked the clinical part of our program with the price negotiation part.

PARTNERS has negotiated directly with over 30 pharmaceutical manufacturers to obtain discounts on the volume of medications used by our nationwide network of HMOs. These discounts were obtained by integrating clinical information concerning the value of medications with cost information.

Because PARTNERS has been successful in driving prescription volume by influencing physician prescribing behavior, by establishing ourselves as credible drug experts, by establishing ourselves as reputable pharmacy researchers, and by building an information system which guarantees data integrity, manufacturers have been persuaded to participate in our volume purchasing program.

I might add that when we began the program 4 years ago, only two manufacturers were participating in the program. But through building a relationship of mutual trust and respect between the pharmaceutical industry and managed care, we have grown the volume pricing program to over 30 manufacturers.

In conclusion, I would like to say that PARTNERS feels that we have a responsibility to manage health care and deliver high quality pharmaceutical benefits at an acceptable cost. To formulate this strategy, we have balanced the internal and external forces affecting drug decisions. This has not been a trivial task and I think the work before this committee is certainly immense.

What you will need is a creative management effort that has been guided by the business model that we have presented today.

To summarize, we at PARTNERS believe that the managed care models and principles that we have tested and proven, building cooperative relationships, establishing a clinical management function, establishing a good relationship with the pharmaceutical industry and pursuing volume purchasing, and by funding efforts on research and development—I really believe that this committee can pull from the ashes the Medicare catastrophic bill and establish a drug program that is affordable and is of high quality for elder Americans.

Thank you, and we look forward to helping you in this effort.

[The prepared statement of Dr. Wilkins and Dr. Schmidt follows:]

WRITTEN TESTIMONY
OF
NORRIE WILKINS AND DONNA SCHMIDT
PARTNERS NATIONAL HEALTH PLANS

In response to the committee's request, we are submitting background information on the business model used by PARTNERS National Health Plans to manage pharmaceutical expenses within a managed care environment. The information presented is based on our experience in managing the pharmacy benefit for our 2,000,000 HMO and PPO members in 33 states.

I. BACKGROUND

PARTNERS is the unique and exclusive joint venture between AEtna Life Insurance Company and VHA Enterprises, Inc., a subsidiary of Voluntary Hospitals of America, Inc. (VHA). PARTNERS started in 1985 with 35 employees, one client and 3,381 members. Four years later, it has more than 2,500 employees, 10,800 clients and 2.2 million members in 33 states.

PARTNERS major goal is to work with providers to manage employer's health care costs for their employees. In order to meet this goal, PARTNERS markets two primary products: Preferred Provider Organizations (PPOs) and Health Maintenance Organizations (HMOs). In 1985, PARTNERS PPOs served one metropolitan area; as of today, we serve over 100 areas with more than 980,000 members. PARTNERS entered the HMO market in 1986. Through a combination of acquisitions and development, we currently manage 33 HMOs with an enrollment of more than 1,125,000 member.

The pharmacy program that we will describe today was first developed and implemented at MedCenters Health Plan in Minneapolis, Minnesota in October 1986 and is currently operational in over 20 of the PARTNERS HMOs. Historically, managed care has not devoted substantial resources for the management and control of drug costs. The primary reason for this lack of attention is that pharmacy expense usually accounts for 5-7% of the health care premium and hospital expense contributes 35-40% of the premium. Therefore, management resources have been devoted to the area of greatest liability (i.e. hospital).

In the last five years, some IPAs, Networks and most staff model HMOs have developed managed care systems which have taken advantage of the cost containment practices in attempting to control drug expense. These cost containment practices include:

. Formularies (list of reimbursed medications)
. Mandatory generic substitution (or Maximum Allowable Cost: MAC)
. Drug utilization review (DUR)
. Volume purchasing with drug manufacturers

Managed care systems which have implemented some or all of the above steps have begun to influence prescribing behavior so that physicians, pharmacists, patients, pharmaceutical manufacturers and insurers now have the incentive and responsibility to work together in a cohesive manner. The goal of managing drug costs and improving the quality of overall drug use constitutes a true managed care system.

II. PARTNERS PHARMACY MANAGEMENT BUSINESS MODEL

PARTNERS pharmacy program's mission is to be the industry leader in managed care pharmacy, providing quality drug therapy for our members while containing member health plan's costs and producing a profit to PARTNERS. PARTNERS in Pharmacy Management (PPM) has identified these key factors which have contributed to the increasing spiral of drug costs and the problem facing the American public today of the wasteful use of medications:

- Inflation - we have consistently seen average prescription cost increases of 1.0% to 1.5% per month.
- New drug technology - pharmaceutical manufacturers introduce new drugs which are considerably more expensive than replacement therapy:
    1987 - New drugs cost an average of 32.54% more than replacement therapy.
    1988 - New drugs cost an average of 48.87% more than replacement therapy.
- Patient demand - advertising of new medications has created a perceived demand for expensive new drugs - Seldane, Tavist-D, Voltaren, etc. when less expensive and equally effective medications are available. The copayment structure of the drug benefit has insulated patients and physicians from prescription prices.
- Physician prescribing - the drug industry spends millions of dollars yearly to influence physician prescribing.

The business model adopted by PARTNERS to control and manage the pharmacy benefit was to implement a strategy which controls cost at the key areas described above, maximizes provider contacting nationally, allows flexible employer benefit options, balances the effects of pharmaceutical industry detailing and improves the standards of prescription drug use throughout the PARTNERS network. Pharmaceutical managed care systems must be able to control drug costs by establishing a management program that addresses each influencing point of drug use and associated costs; therefore, the PARTNERS model was built to support and maintain strong balanced relationships between these influencing factors:

- Pharmaceutical manufacturer
- Physician/Prescriber
- Patient
- Pharmacist

III. CLAIMS PROCESSING

To better manage, PARTNERS has developed a one-of-a-kind, technologically advanced information processing system, using a relational database structure. By monitoring factors such as member eligibility, quantity of a particular drug dispensed, diagnosis and ingredient costs for each claim, PARTNERS can further help maintain tight control over pharmacy claims costs. Perhaps the system's most valuable feature is its flexibility. We realize that each HMO, each employer group and each pharmacist operates within a different set of parameters, each plan has different benefits levels. Furthermore, to detect problems and establish plans of action, the system features fraud and abuse monitoring.

IV. CLINICAL PROGRAMS

A. Goal

The goal of the clinical services division of PARTNERS in Pharmacy Management is to provide a method for defining, assessing and improving the efficacy, safety and cost of drug usage in the members we serve. Objectives of the clinical staff include the following:

- To establish rational prescribing (correct drug, patient dose, etc.)
- To minimize needless expenditure of resources by eliminating care which does not increase quality or improve outcome.
- To increase physician awareness of efficacy, safety and cost issues of drug therapy.
- To serve as a research team to oversee and prevent aberrant prescribing and intervene if an incident of undesirable outcome becomes apparent.
- To redefine and/or develop reporting systems.

B. Pharmacy and Therapeutics Committee

PARTNERS in Pharmacy Management utilizes a National Pharmacy and Therapeutics (P&T) Committee to administer the pharmacy benefit in a managed care setting. The committee consists of at least three plan physicians, a medical director, two registered pharmacists and an administrator. Issues that the P&T committee address and serve include:

- Serving in an advisory capacity to the plan physicians and the plan itself in all matters pertaining to the use of drugs.
- To develop a formulary of drugs accepted for use in the plan and to provide for its constant review.
- To establish procedures and programs that help ensure cost effective drug therapy.
- To participate in quality assurance activities related to the distribution, administration and use of medications.
- To review adverse drug reactions occurring throughout the plan.
- To initiate and/or direct drug use review programs and studies and review the results..
- To advise pharmacies and providers in the implementation of effective drug distribution and control procedures.

C. Formulary

PARTNERS in Pharmacy Management implements a formulary management process for its plans as a measure to help restrain pharmaceutical costs. The proliferation of drugs with similar indications but large variations in cost has caused a disproportionate increase in drug expenditures. The formulary is designed to promote rational drug therapy through inclusion of drug products which have been selected based upon therapeutic efficacy, relative freedom from side effects and cost. The formulary represents a list of drug products that are reimbursed by the health plan. All new drug entities will not be reimbursable until they are reviewed by the Pharmacy and Therapeutics Committee.

A negative formulary, which lists drugs not reimbursed by the health plan, is also distributed to plan providers. Alternate choices to negative formulary items are listed as a convenience to the physician. A formulary program enhances the quality of patient care while containing costs.

D. Generic Substitution

Through its formulary management process, PARTNERS mandates the use of generic substitution by enforcing a maximum allowable cost (MAC) program. In order for a drug to be placed on the MAC program, these criteria must be meet:

1. Contain the same active ingredients as the brand name drug. That is, it must have the same chemical in it, but the non-active ingredients like "fillers" or color may differ.
2. Be identical in dose, form and method. That is, it must have the same amount of drug, in the same form, such as a tablet, to be taken by mouth.
3. Have the same uses, cautions and other instructions. That is, it must be labeled in the same way and be used for the same reasons as the brand name drug.

4. The time to absorb and the amount absorbed must be nearly the same. Also, the total amount of drug that enters the bloodstream must be the same for both the generic and the brand name drug.
5. Meet the same batch consistency requirements for identity, strength, purity and quality. That is, each batch of drug mixed up by the generic drug company must meet the same requirements to ensure that you are getting the same product each time.
6. Must be manufactured under the same strict standards of the FDA's Good Manufacturing Practice regulations as required for brand name drugs.

E. Therapeutic Substitution

Therapeutic substitution is the use of different chemical entity prescribed for the same disease process to effect the same outcome. Pharmaceutical manufacturers have made "therapeutic equivalent" drugs for years and supported studies comparing two different drugs for the same diagnosis. Physicians have always practiced therapeutic substitution when writing a prescription. The controversy now is whether pharmacists can practice therapeutic substitution with or without a physician's approval. Only one state, Washington, allows therapeutic substitution by law. PARTNERS National Health plans does not mandate therapeutic substitution by the pharmacist. However, in certain instances PARTNERS requires the pharmacist to call the physician to request an order change.

The physician can then decide whether to prescribe a therapeutic equivalent which would be reimbursable by PARTNERS. If, however, the physician does not agree that the therapeutically equivalent drug will not result in the same outcome, (s)he has two options:

1. The physician can maintain that the patient needs the first drug and the patient must pay full price, or
2. The physician can write a letter of exception for medical reasons to PARTNERS. If there is a true medical necessity, PARTNERS will pay the cost of the first drug minus the copay.

Examples of therapeutic substitution would be the anti-ulcer drugs Tagamet, Zantac, Pepcid and Axid. All these drugs are equally effective for the treatment of duodenal ulcers, and side effects are rare. Therefore, cost should be the major factor in the physician's decision. Another example are beta blockers for hypertension. For some patients who do not experience side effects, any beta blocker would be as effective as another.

F. Drug Update

The Drug Update is a monthly one-page newsletter to provider physicians as an educational tool to promote better prescribing. This newsletter is an extension of the formulary and is written by pharmacists and physicians. Many decisions by the Pharmacy and Therapeutics Committee on drug coverage and use are communicated officially to provider physicians in this manner. Important therapeutic issues such as hypertension, heart disease and lowering cholesterol are researched, condensed and edited by physicians in that specialty. Results of drug use evaluations are reported. The majority of physicians are already looking for methods to improve their practice and this newsletter can help them learn to use drugs more efficiently.

G. Drug Utilization Review

PARTNERS in Pharmacy management has the capacity to access multiple databases to produce standard and specialized reports. This function enables Medical Directors, Executive Directors and their staff to track pharmacy utilization in a variety of ways. These reports and the information system are used to support clinical decision making by this iterative process:

- Analyze prescribing trends
- Predict impact of prescribing change
- State objective of the UR effort
- Develop criteria to support rational prescribing
- Collect and analyze data
- Evaluate the impact
- Report results

V. VOLUME PRICING

PARTNERS has negotiated directly with over 30 pharmaceutical manufacturers to obtain discounts on the volume of medications used by our nationwide network of HMOs. These discounts are obtained by integrating clinical information concerning the value of medications with cost information. Because PARTNERS has been successful in driving prescription volume, influencing physician prescribing behavior through counter detailing efforts, establishing ourselves as credible drug experts, reputable pharmacy researchers, and by building an information system which guarantees data integrity, manufacturers have been persuaded to participate in our volume pricing program.

Building a relationship of mutual trust and respect between managed care and the drug industry has been an important objective of the PARTNERS pharmacy program over the last four years. Managed care practices clearly represent fundamental change for the drug industry from past historical practice. Our strategy in building new working relationships between our two industries has been to foster open discussion and understanding. There have been several drug companies that have been outstanding in their efforts to learn the managed care industry and to adapt their business strategies to participate in a manner where both industries (managed care and pharmaceutical) take responsibility for providing quality drug therapy at an affordable cost.

VI. RESEARCH AND DEVELOPMENT

PARTNERS goal is to be a ground-breaking leader with solid solutions to the health care questions of this century, and to influence the direction of managed care into the next century. With this goal in mind, PARTNERS is committed to the ongoing study of improved pharmacy managed care models. Four research efforts currently in process at PARTNERS are helping us achieve this goal:

The Hartford Grant - to study the effects of drug information to HMO providers on high-risk, elderly patients. This grant was awarded by the Hartford Foundation to the University of Minnesota and American MedCenters (now PARTNERS National Health Plans) in the fall of 1986. It is a three year study with the final report due in December 1989. The objectives of the study are to look at the drug problems in a senior population, establish if/how physician prescribing contributes to those problems and how we can change physician behavior and what effect this will have on the overall health care.

H_2 Blocker Study - The objective of the study is to understand whether, through a formulary decision making process, we could identify only one of the antihistamine antagonists to be on our formulary (Zantac, Tagamet, Pepcide). The study compares the usage of these drugs in terms of cost savings of drug and hospital stay.

Community Pharmacist Project - A feasibility study is in place to examine how we can use the community pharmacist to promote more active patient accountability for proper medication use.

Analytical Rating Tool (ART) - ART is a tool used by PARTNERS to identify the various steps in the formulary decision making process. This tool allows us to justify formulary decisions in a consistent and clinical fashion, and it promotes discussion between pharmacists and physicians as to the relative worth of similar medications.

VII. PROGRAM EVALUATION

PARTNERS has a responsibility to manage a health care system that delivers a high quality pharmacy benefit at an acceptable cost to patients and payors. To formulate a pharmacy managed care strategy, we have balanced the internal and external forces affecting drug decisions. Balancing these concerns is not a trivial task, but a creative management effort that has been guided by the business model presented today at this hearing. PARTNERS has been successful in documenting not only improved financial management but also, and more importantly, we have documented that the quality of pharmaceutical care has improved for our patients.

At MedCenters Health Plan alone the program has saved over 5 million dollars in less than four years in drug costs and administrative costs. These savings were achieved by bringing together professionals and industries, that traditionally have not been able to work together, in a managed care environment which fostered and supported cooperative working relationships. In other HMOs around the United States, we have documented financial and quality of care differences in prescribing practices that are at times staggering. We at PARTNERS are hopeful what we can assist this Committee in molding the architecture we have proven to be successful into a national health care system that will provide improved quality of drug use at an affordable cost for all Americans. We sincerely thank you for the opportunity to present the PARTNERS business model to this important committee.

The **Chairman**. Thank you very much, Dr. Wilkins. I see Senator Kohl entered during your statement. Senator Kohl, would you like to make a statement or ask a question at this time?

STATEMENT OF SENATOR HERBERT KOHL

Senator **Kohl**. Senator Pryor, I did want to stop by and say a word.

The **Chairman**. I understand you are in a Judiciary hearing at this time.

Senator **Kohl**. Yes, thank you, Mr. Chairman.

I am pleased to be able to stop by and express my admiration for all you have done and the efforts you have put forth on behalf of the poor and the elderly of our Nation. Those efforts have already made a significant difference in the lives of many Americans. I and many other people are deeply grateful to you for your years of service.

A solution to the skyrocketing problem of prescription drug costs is critical to our effort to provide universal access to health care in this country. I am particularly concerned that with changes in the catastrophic health care law that millions of low income elderly and disabled now are going to have it socked to them, and socked to them good.

It is an embarrassment that many of those who are in desperate need of therapeutic treatment may even have to go outside the borders of our own country to get reasonably priced prescription drugs.

I am struck by the absence of the prescription drug manufacturers. I am appalled by the apparent lack of desire on their part to be a part of the solution. For those of you sitting in this room who are part of the pharmaceutical manufacturing industry, I think you need to take back the message that there is an open invitation to work out these problems in a civil and cooperative manner. But you need to know also that our patience is not infinite. We all hope that we will see a bit more cooperation in the very near future on your part.

This Senator fully supports the committee's efforts to turn a bad deal into a fair deal. Senator Pryor, my deepest respect and appreciation goes to you for all you have done.

The **Chairman**. Thank you, Senator Kohl, thank you very much. Senator Cohen.

Senator **Cohen**. Mr. Berryman, can you tell us what the rationale is for such discrimination in pricing that occurs in Virginia? You indicated, I believe, that it was 1 cent per 100-packet for one State agency, and that rose to as much as $1 at a sister agency? How do you, as a pharmacist, account for that kind of price discrimination?

Mr. **Berryman**. Senator Cohen, I can't account for it. The industry has to account for it. In Virginia, the Medicaid department ends up paying retail price for the product. The industry has many classes of trade which you as the Congress have permitted under the Robinson-Patman Act.

There are numerous classes of trade out there, managed health care happens to be one of them. It is now becoming one of the major ones.

For-profit nursing homes, not-for-profit nursing homes, for-profit hospitals, not-for-profit hospitals—they are all treated the same within their particular class of trade. The industry does not recognize a retail class of trade, and that happens to be Mr. Baskin's and my problem at the retail drugstores.

I can't answer that question for you, other than to say that the retail class of trade is not recognized. I think one of the possible solutions is that you use your influence to at least require the industry to recognize the Medicaid Program across the country as a managed care program. If so, my interpretation of what is going on would qualify Medicaid for the pricing. There is nothing much more managed in this country than Medicaid. It certainly is that way in Virginia. We have a very efficient program.

Senator **Cohen**. Can you give any kind of rationale in your own mind as to why there might be such a differential between what is charged to a hospital and what is charged to a consumer who is out of the hospital, at a local pharmacy?

Mr. **Berryman**. Again, that is a question that the industry ought to respond to. My opinion is that it started out a long time ago, with Veterans hospitals and nonprofit facilities, during World War II, possibly. It has now been expanded into what the industry perceives, I believe, as a very effective marketing tool.

If they can give their product away and get it on a managed care formulary or a hospital formulary, then those products are written for as they go out into the marketplace at the higher inflated cost of that product. You and I know that it costs them more than a penny to make a nitroglycerin patch. That's pretty obvious. But I think that is the strategy behind it, sir.

Senator **Cohen**. Mr. Baskin, your program only applies to Medicaid, is that correct?

Mr. **Baskin**. No, sir. Our program is for retail pharmacies. What I was describing was our chargeback system which can be used by Medicaid patients.

Senator **Cohen**. Does that mean, for example, that Mr. Green, who is not on Medicaid, could be a beneficiary under your system?

Mr. **Baskin**. He could very well be a beneficiary of it if the manufacturers were within our buying group, which has 2,200 retail pharmacies out there. He would be a beneficiary of it, yes. I was just asked to describe how our system could be used for Medicaid.

Senator **Cohen**. I got the impression, reading your testimony that a list of the Medicaid recipients had to be submitted to the manufacturer, so they would know whether the drug was actually going out to those who could not afford it.

Mr. **Baskin**. What would happen would be that the Medicaid department, once they had paid a local pharmacy for that prescription, would bill the manufacturer for the appropriate number of units. If you dispensed 100 tablets and there was a $4.00 chargeback, that would give them some assurance that it was used just for Medicaid patients. The pharmacist would not be involved in that.

Senator **Cohen**. I would like to ask both you and Dr. Wilkins—how does the formulary work if you have only one effective drug?

Dr. **Wilkins**. If there is only one effective drug for the treatment of a specific disease?

Senator **Cohen**. We have heard some testimony that there is only one effective drug for Mrs. Bivens. What do you do in that situation, where you have in effect a monopoly, where the drug manufacturer does not have to deal with you?

Dr. **Wilkins**. In that case, we would use part of our clinical drug program utilization review to see if this drug, which is very expensive, is the only drug to treat a particular disease. Then we try to establish rules and systems to make sure that the drug is only being used for that particular disease. If there is only one drug, then you are correct, the drug company has a monopoly, however, there is much one can do and should do on an ongoing basis to ensure proper and appropriate use of that medication, especially since there may be nondrug alternatives for treatment.

Senator **Cohen**. Mr. Berryman, you talked about the State taking some action. I was curious as to why the State has not acted sooner, if you have that kind of differential between one State agency that is purchasing drugs at a higher price level than the other. You talked about the proposal of a rebate program. Is that similar to Mr. Baskin's program?

Mr. **Berryman**. No, sir. During the last session of the General Assembly, the Medicaid department was mandated to come up with, by the Appropriations Act, $5,500,000 in cost savings. One of the proposals that was submitted by that department was to request manufacturers to rebate 5 percent, I believe, of the sole source products that Medicaid currently pays for.

We have had a 71-percent price increase on drugs in the last 4 years. Sole source products make up 87 percent of the dollars spent in our Medicaid program and only about 57 percent of the prescriptions written for, but 87 percent of the dollars. It just seems that it was really a takeoff on the chargeback mechanism. It was simply saying "How about sharing in the burden?" We were quickly reminded that there was not statutory authority for such a rebate program in Virginia, and we could not require it.

Senator **Cohen**. Has your legislature been advised that if there is any question as to the authority to have a State-by-State chargeback program, you can run under the Commerce Clause, for example?

Mr. **Berryman**. In my written testimony, Senator Cohen, I think there is reference to the Virginia State House Committee Bill 403, which is studying the Medicaid Program. They are now looking at, I believe, ways to come up and develop that and have an attorney study that to see if it is possible to initiate that kind of program. Then if we need some statutory legislation passed in Virginia, then we would like to do that.

It is possible that this Congress needs to countenance that idea—I am not an attorney—because it may be that it is not just a State problem. It may be a State and a Federal problem. Perhaps something together needs to be done to make sure that something like that can be instituted.

The **Chairman**. Thank you, Senator Cohen. Those are very good questions.

Senator Cohen, in our last hearing on this issue some months ago on prescription drug prices, we singled out and saluted one Federal agency the Department of Veterans Affairs, for having gone to the pharmaceutical manufacturers directly and said "All right, we buy a lot of prescription drugs, and we are going to buy them at a fair price."

As a result, they do. In some cases, we see Medicare paying for the same drug, the same number of capsules or tablets, and quantity, from the same manufacturer, but at a price that is four to five or even six times higher than the Department of Veterans Affairs. Why does the Department pay less? Because they negotiate. They have brought the pharmaceutical manufacturers to the bargaining table, and as a result, they have seen tremendous savings.

I have even suggested off hand and informally that we turn all of the drug buying for the Federal Government over to the Department of Veterans Affairs. Everybody laughs, but I don't see why they should. It would probably save us multi-millions of dollars.

But outside of the Department of Veterans Affairs right now we are not exercising the leverage we have.

I want to quote some material about doctors from a New York Times article in the Magazine section of November 5, 1989, that is related to some of the problems we have talked about today.

" 'I can get any drug on the university hospital formulary,' says a territorial sales manager for one pharmaceutical company. 'I just find some fertile soil, the right person who is hungry for research money, doesn't matter what the side effects are or if it four times the price of an equally good drug. I know the researcher will help me get it on the formulary in exchange for research money.' "

I think what we have here is a cycle of dependency where drug manufacturers do anything to get their products on a formulary including taking advantage of university hospitals need for research money. Dr. Wilkins, is it that easy for a drug manufacturer to get his drug in your formulary?

Dr. **Wilkins**. It would be appropriate for Dr. Schmidt to answer that question.

The **Chairman**. Dr. Schmidt.

Dr. **Schmidt**. I want to reiterate about the formulary. It is not just for drug manufacturers to get their drug on the formulary. It is also for the physicians to choose the drug. So the physicians are quite involved in our pharmacy and therapeutics committee, saying which drugs we shall use. To me a formulary is not a list of drugs that prohibits physicians from prescribing what they want, it is a guideline for good drug therapy and quality drug therapy for patients.

So we use the medical authority of a large group of physicians to say if it is a valuable drug to put on the formulary.

Senator **Cohen**. Can I ask if there is any system to check whether the physicians get free drugs?

Dr. **Schmidt**. Yes, enclosed in our packet, we do have an ethics policy for our pharmacy and therapeutics committee. At least in our national and some local P&T committees, they have to disclose what research they have, and what moneys they have received and what trips they have taken.

Senator **Cohen**. So the physicians are not just receiving free drugs to dispense to their patients, and then also promoting those for the listing on the formulary?

Dr. **Schmidt**. Well, I can't say that they don't take free drugs. The drug company representative can give them samples that they can give to their patients. We allow that. But we do take into consideration who should be voting on a particular drug issue.

Senator **Cohen**. Thank you.

The **Chairman**. On that point, Dr. Schmidt, let me ask you this. I'm still back in the New York Times magazine section, of November 5. The article is called "Pitching Doctors." I am quoting—"One company, Pfizer Pharmaceuticals, requires sales representatives to tote"—I thought that was a Southern word, tote—"laptop computers into which they enter data on each doctor visited, including notes on his personality, his nurses' and receptionists' names, birthdays and hobbies of key people in the office."

"This information is relayed to the company's central computer for use in future efforts to shape an individual doctor's prescribing habits."

Further in the article, "As one detail man explains, 'where there are eight drugs that are equally good, the doctor makes a choice based on nonscience. If I drop off samples, pens, other devices, the doctor will write for my product and not the other guy's.' "

Is this still going on?

Dr. **Schmidt**. I would have to say yes. I hope that doctors, at least as a large committee on the pharmacy and therapeutics committee, will look at whatever drug is effective, whether it has less side effects, and if those two things are equal, less costs.

So when you say equally effective, to me that is only part of the picture. Side effects, availability and cost go in there. We try to say that if there are eight drugs that are equally effective, then what about side effects? What about long-term outcomes? Are we going to use all the resources or more resources with one drug than another?

Those are the questions that are looked at by pharmacy and therapeutics committees, and those decisions are communicated by the newsletter to individual physicians. They are really taking those decisions as leadership from their peers, for example, nephrologists, for hypertension, to say what therapy should guide their practice.

Dr. **Wilkins**. I would like to comment that yes, indeed, the detailing efforts that the pharmaceutical manufacturers have on the physicians is real and is effective in having physicians select certain products. A term we use in managed care to balance those efforts is called "counter-detailing." We prepare the drug update, or the drug information that we send to our physicians, in an effort to balance what we know the pharmaceutical industry might be saying related to a certain product.

In our HMO environment, it is not unusual for a drug representative to give a message to a physician that their product is better in some way. Our physicians carry their PARTNERS formulary in their pocket. It is not unusual for the physician to pull out the formulary and say "Well, I hear what you are saying, representative from the drug company, but according to the policies and recommendations of the PARTNERS Health Plan, that is not true."

What we are trying to say here is that PARTNERS has developed a very good working relationship and a trusting relationship with our physicians so that our information and policies are supported by the physicians.

The CHAIRMAN. Dr. Wilkins, while you are speaking let me ask this. You supplied the committee with some very interesting tables.[5] I would urge my colleagues Senator Kohl and Senator Cohen to look at this table. It says that in 1987, new drugs cost 33 percent more than the old drugs they replaced. By 1988, they cost 49 percent more than the old drugs they replaced.

I would like to know your source for the data. I am not questioning it, I just think it's fascinating. In your opinion, are these new drugs worth that much more than the old drugs they replaced?

Dr. WILKINS. Mr. Chairman, that information was compiled by the pharmacy claims information of the PARTNERS National Health Plans has. Those were on actual paid claims.

Those increases really are phenomenal, especially in a managed care environment, when you can't raise your premiums that high without losing a significant membership. We view this as a significant problem.

When a new drug is announced, we go through a very sophisticated, clinically justifiable process to evaluate the worth of that medication. In many cases the increased cost of that drug is not worth the value. In those cases we make a policy decision to either not cover the drug, or to restrict the drug for a very narrow market.

The CHAIRMAN. The Food and Drug Administration—are they right or wrong when they say, in their assessment of 84 percent of the new drugs, that they have little or no therapeutic potential to improve on existing drug therapies? Is that right or wrong, or near right, or do you have any way to judge?

Dr. WILKINS. I am a pharmacist, so I will put that hat on. I am not sure that I agree with 84 percent, but I agree that the number is quite high.

Dr. SCHMIDT. What we usually do is take a look at what the FDA has classified as 1C or little or no therapeutic gain over existing drugs. We will put that on our excluded drug list unless physicians come to us and say "This is something that we really need, even though it is classified 1C." It is rare that the physicians come to the pharmacy and therapeutics committee and say that. So I would say, yes, it is very high.

The CHAIRMAN. Let's go back a moment to Mr. Baskin's testimony.

I think from your testimony, Tery, you said drug manufacturers seem to be a little more willing to negotiate the price of multiple source drugs—those drugs without a patent—with retail pharmacies who buy in groups. What do they do about the patented drugs, do they negotiate those?

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[5] See p. 758.

Mr. **Baskin**. Basically, they do not. Less than 10 percent of our 1,600 items are brand name drugs. Very few of those—we have 137 exactly—and very few of those are true single source drugs. Those were obtained by getting a bid from a company of all their product line. We had something they wanted, and we said to get that they would have to bid their entire line. But for the most part they do not.

That brings up an interesting question Senator Cohen asked a while ago, about why we feel that this is not happening. It is interesting to me that Congress created some classes of trade, and it is allowing all this discriminatory pricing to go on, yet the largest purchaser out there, the Medicaid program, can't seem to access it. That is an interesting dichotomy to me.

Dr. Wilkins talked about the fact that they are getting these prices. In my testimony I stated that it is not just a volume issue. In our program we are purchasing in excess of $300 million worth of prescription drugs. That ought to be enough volume—I'm not sure what her volume is—but I know in a number of cases, for instance in a small HMO in north central Arkansas, I doubt if they have 5,000 people covered entirely. So it is not just a volume issue.

There is something I wanted to elaborate on. This was something that was said to me by a government affairs representative of a company. This person was very new on the job, as a matter of fact this was the first call this person had made. We were discussing a variety of things and I asked through what I thought was a stimulating question and asked why companies like hers did not bid the Medicaid Program. She said that they would be blackballed immediately. They could not do that. If they were the first company to do that, there would be no way of telling where it would stop.

I thought that was an interesting twist.

The **Chairman**. What did she mean by "blackballed"?

Mr. **Baskin**. Well, I guess that's subject to interpretation, but obviously she was saying to us that her company could not afford the heat from the sister companies if they happened to open this dam, if you will. You talked about the situation in California in your opening remarks, that if it started in California, there is no telling where it would end up. There are some real market issues there.

Dr. **Wilkins**. Senator Pryor, may I respond? I would not call the volume program we have discriminatory, but differential. It is not only based on volume, it is based on the fact that our clinical programs are actually affecting the kinds of medications that are selected and dispensed to our patients. It is differential. The managed care environment has something to give to the pharmaceutical industry, and that is market share.

I think in defense of the pharmaceutical industry, having worked with them for over 4 years, it is true that there are one or two that started, and then it took a lot of my time and a lot of time of the staff people at PARTNERS to represent our industry to them, so that they could understand our objective and develop that trust and design win-win strategies.

All I am saying is that once you develop that trust, there is the opportunity to build programs like this for Medicaid programs.

The **Chairman**. Mr. Berryman, you have testified very eloquently on what is happening in your State, and how you have had to cut back on programs because the legislature mandated cuts. You have had to take a $5,500,000 out of Medicaid, is that correct?

Mr. **Berryman**. That's right.

The **Chairman**. Let's go through this list and find out who is participating in the burden sharing of cuts. The pharmacists?

Mr. **Berryman**. In Virginia, pharmacists have had to accept one fee per month on their prescriptions, so they took their hit.

The **Chairman**. Hospitals?

Mr. **Berryman**. Hospitals are already reimbursed at cost. And some of them would contend less than cost.

The **Chairman**. Nursing homes?

Mr. **Berryman**. They are impacted somewhat on the drug program.

The **Chairman**. What about doctors?

Mr. **Berryman**. In our Medicaid program, we have had to go back to the last two sessions of the General Assembly to get appropriations to get their fees raised. They are now at the 15th percentile, and in the next year they will go the 21st percentile.

The **Chairman**. What does that mean?

Mr. **Berryman**. Reimbursement of their usual and customary fees. That's a major problem in Virginia. Because of our inability to pay them properly, we have had physicians drop out of the program. In southwestern Virginia, which is very rural, in Abingdon, VA, we have no OB people to deliver babies now. At one time we had a problem in Danville, VA, which is a fairly good sized community, with no pediatric care.

The **Chairman**. Let's go to the Medicaid recipients, Mr. Berryman. Are they are part of this?

Mr. **Berryman**. Medicaid recipients had their co-pays increased this time.

The **Chairman**. So they are participating in the cuts.

Mr. **Berryman**. Yes, sir.

The **Chairman**. What about the drug manufacturers?

Mr. **Berryman**. To date, the only thing I can say about the drug manufacturers is that the transdermal nitroglycerin patches, and all transdermal delivery systems were taken off the program because we did not feel like the technology was worth the price of the product. I think that's basically the way the legislature felt about it. That was a legislative action.

So if there has been a hit, that has been the only one.

The **Chairman**. Mr. Berryman, at this moment, I am going to yield to Senator Cohen and Senator Kohl, and let them ask any questions, and I will return in about 3 minutes.

Senator Kohl.

Senator **Kohl**. On the one hand, you have, Mr. Berryman, the manufacturers. They distribute the product, they have their enormous influence and leverage, and they have their ways of communicating with each other, at functions and trade associations, it is obviously a very vast and powerful manufacturing and distribution system that has as its goal making as much profit as they can, which is what they are supposed to be doing.

On the other hand, you have these powerful consumer organizations. Don't you think what we are missing in the country, and I think that's what we are discussing today, is the amalgamation of these powerful organizations, to see that we get a price that is a fair price, and that we are not simply doing a job at that level of working with each other and using our enormous power and influence to get the job done?

Mr. **Berryman**. I agree with you, Senator Kohl. To a degree the strategy has been to divide and conquer. The pharmacists are on their own and don't have the ability to fight the manufacturers in this country, or in the State of Virginia. Although when we start talking about a restricted formulary, it does not take long for their industry to have all their representatives in Virginia talking to the doctors that they call on, and saying "Guess what they are trying to do to you at the legislature and at the Medicaid department, they want to restrict the formulary, and you can't prescribe just anything you want anymore."

Although many of those physicians are working under a formulary in a hospital where they have privileges. But they, the industry, have the ability to quickly respond and to use their representatives in the field to market against whatever Medicaid wants, or the legislature, or whatever they might do to lobby against it. It is a very difficult force.

When you can't communicate substantively, it is difficult to resolve problems.

Senator **Kohl**. I don't think sometimes we are as aware or as sensitive to the enormous power that we have as users to influence the price, if we just use our enormity intelligently. If we don't of course, you could make an argument that we have no cause to blame the manufacturer, he operates in a free market economy and he has a right, within law, to make as much as he can and should. But if we don't organize ourselves to see that we get the best price on the other end, that is not his fault, that is our fault.

What do you think, Dr. Wilkins?

Dr. **Wilkins**. I would agree there. Especially in a managed care environment, we do have the opportunity to evaluate drugs and to make decisions as to their worth. It was our responsibility to do that, and once we have done it, we now have the ability to negotiate. On the other hand, I believe manufacturers have the responsibility to be socially responsible especially for a national problem like making health care affordable.

Mr. **Baskin**. As far as the ability to use a formulary in my pharmacy in North Little Rock, AR, we have a formulary in my pharmacy. The physicians that I work and practice with, there are certain drugs that we use, and that we don't use. We decide those things. We go through a much more informal process than Dr. Wilkins is describing, but it is the same type of thing.

You are absolutely right, if the purchasers would use their leverage, it's amazing what they could do. I think that is what you are all looking into, your being the Federal Government and using our money, you are one of the biggest if not the biggest purchasers in the country. I am trying to figure out why the Arkansas State Health Department, that I work as a consultant for in North Little Rock, is paying 42 cents for their birth control pills, and my same State government, through the Medicaid Program, they are paying $15 and up for the same pills.

Somewhere someone is not carrying their own weight. What I would like to see is for the prices to be levelized. If you are going to use a product, if there are costs incurred in that, then you should bear those costs.

Senator **KOHL**. Then I guess you could make an argument, and I am not, but you could, not to blame the manufacturer if one person is willing to pay 42 cents and the other person pays $15—that's the way the market works, right?

Mr. **BERRYMAN**. I would like to interject, that it seems to be that practically, because of the class of trade, any managed care group can get rebates or whatever. But I think the record of your staff committee will show that in Maryland and Kansas, that they did ask the manufacturers to bid the Medicaid Program and they did not.

So everybody doesn't have equal access to the bids.

Dr. **WILKINS**. I would argue that unless you have linked your clinical program with your price negotiations that you really don't have the power to obtain volume pricing. I don't know the Medicaid Program, in the two States you mentioned, but if they are missing that part, they are not the same kind of buyer as a managed care entity.

Mr. **BERRYMAN**. We just had approved in the Virginia Medicaid budget $500,000 to implement such a program, and we shall soon see if your statement is correct.

Dr. **WILKINS**. The other point, Senator Kohl, is does the pharmaceutical manufacturer have the right to charge whatever they want, and whoever pays for it, that's just free business? I guess my response there would be that we all have such a tremendous responsibility to get a handle on the costs of health care in the United States that I don't believe anyone can take that sort of action lightly any more.

Senator **KOHL**. I don't want you to think that is necessarily my position—it isn't my position—but when you live in a free market economy you always have to recognize that the person who manufactures a good just tries to do as well as he can. That's not un-American. It may not be what we want. It seems to me that our power, at the other side, is not being used successfully to hold down the costs of drug increases. We can't just blame the manufacturer. That isn't going to get us anywhere.

Dr. **WILKINS**. That's true.

Senator **KOHL**. I am not suggesting we are. That kind of attitude would not get us anywhere, if we had that attitude.

Dr. **WILKINS**. I think that's true, also in managed care, where the purchasers of managed care, the employers and patients, are demanding that managed care document and justify its prices. That kind of balance is good. The more we can create that balance, all of us would benefit.

The **CHAIRMAN**. Senator Cohen.

Senator **COHEN**. Mr. Berryman, first of all you indicated that once the legislature started to consider various proposals, the drug manufacturers contacted the physicians and said "Look what they are trying to do to your medical practice. You are not going to be able to prescribe this type of drug and get reimbursement for it."

Mr. **BERRYMAN**. That's correct.

Senator **Cohen**. The consequence is a lobbying effort being made by the local doctors or the AMA, is that what takes place?

Mr. **Berryman**. It is fair to say that physicians don't like restricted formularies under any circumstances. They live with them in hospitals. They do fine. I run a hospital pharmacy and the formulary is not a problem. It is inconvenient for them to have a restricted formulary in their outpatient practices.

Senator **Cohen**. Why is that?

Mr. **Berryman**. Basically because they have to remember that they can't use certain products for certain insurance programs, and it's a very difficult situation because various programs would pay for different products, and they are not the same. It is not universal. That is true in the Medicaid Program.

Senator **Cohen**. Don't most physicians' offices now have those little computers? I think Senator Pryor was talking about laptop computers——

The **Chairman**. I was quoting the New York Times.

Senator **Cohen**. Don't most physicians' offices have a computer into which everything is logged? If you have such and such a drug, you will get reimbursed under the following—you punch a key and it prints it out?

Mr. **Berryman**. That's not generally available in a physician's office.

Senator **Cohen**. You don't think that's available in a physician's office?

Mr. **Berryman**. No. I think the technology is there to deliver it, but I do not think that that is generally available in a physician's office.

Senator **Cohen**. They sure have a computer for their billing practices, I can tell you that.

Mr. **Berryman**. That's correct.

Senator **Cohen**. Dr. Wilkins, I would like to come back to the point raised by Senator Pryor in this context. All States are not created equal. They do not have the same distribution of population. They do not have the same capability that other States might have in putting together private groups or PACE's, or whatever such group may be called.

All States do not have the organizational talent, or whatever it might be. They are not all created equal. What would be the major objection to having a central purchasing agency, at the Federal level?

Dr. **Wilkins**. From my perspective, I don't see a major drawback. I think that kind of strategy certainly has some real merits to controlling pharmaceutical costs. However, having managed the pharmacy benefit in 33 States, I can say that each State is also different in terms of their expectations and in getting them to agree on some sort of standard would certainly be a difficult task.

Senator **Cohen**. Dr. Schmidt.

Dr. **Schmidt**. The only obstacle I can see are physicians' local standards of practice are completely different from one State or region to another. So if you were to set up a formulary, that would be bit difficult, to get all the physicians, to agree on what is a good standard of practice nationally for a particular diagnosis.

Dr. WILKINS. However, it can be done. I think a classic example that we have in Minnesota is that in the four major HMO's, there are four different formularies. So our physicians carry four of those little books around, and they don't have computers in their office to keep track of things.

But I do think that any system can account for State variability in terms of the standard of practice. It is definitely true that in the PARTNER system, there are standards of practice that are different, and although we have a national drug formulary, we also have the ability and flexibility to offer differences at the State level.

Senator COHEN. Do you think such a national central purchasing system could be set up with the kind of flexibility that is built in by your organization?

Dr. WILKINS. Yes. Definitely.

Senator COHEN. That's all I have.

The CHAIRMAN. Thank you, Senator Cohen. I have one final question, then I fear we are going to have to dismiss this panel. We will leave this record of the hearing open for 10 days, if there are any follow-on questions submitted in writing to any of the panelists we would appreciate your response. In a follow-on to Senator Cohen's question, I will throw this idea out.

What would happen if Dr. Louis Sullivan, the Secretary of HHS, the members of this committee, the members of the Senate Finance Committee, the Ways and Means Committee and the House Committee on Aging, invited the pharmaceutical manufacturers to this room, closed the door, and said "Okay; enough is enough. We are going to buy these drugs from you but we are going to negotiate a fair price."

What would the response of the drug manufacturers be, given the degree of leverage the Federal Government could impose upon them? What would their response be?

Tery.

Mr. BASKIN. Well, you are asking an opinion question, so I will give you mine.

I think the net result of that would be that you would have something that resembled one price for everybody. I think we have a situation now where——

The CHAIRMAN. Do you think that's good?

Mr. BASKIN. I think it's wonderful. You have a situation where you have a balloon, if you squeeze it on one end, it has to get bigger on the other end, and that is just the simple dynamics of pressing it hard.

The CHAIRMAN. Mr. Berryman.

Mr. BERRYMAN. That might solve your problem at the moment, sir, but if there is nothing, no controls put into place after that, then we just go for another round of filing price increases. I am a free enterprise guy. I own my own business. I don't want to see the pharmaceutical industry controlled to the point that the Government has to set all the prices. But I do think the manufacturers need to be responsible.

I will give you an example. There is a product called Seldane that came on the market. It is an antihistamine that sells for around $60 for 100. It came out 3 or 4 years ago. It has a very low side effect profile, and does not cause drowsiness and Seldane happened to be a drug that is given every 12 hours.

A new product came out on the market called Hismanal. Hismanal can be given once a day and it has the same side effect profile as Seldane. It is priced almost double of what Seldane was. Now you don't have to be a financial expert to see that that is pricing at what the market will bear, rather than what it cost to bring that drug to market, to produce it and develop and market it.

I think you have got to do something to make the industry more responsible in that area. A one-time deal does not give you any savings later on.

The CHAIRMAN. Speaking of that economic theory, pricing at what the market will bear, do you agree or disagree that the market is at that level right now? Are we reaching that point keeping in mind that we are seeing drugs being ordered today from overseas to keep AIDS patients alive, we are seeing a 280 percent increase in the price of Mr. Green's drugs, and we are seeing all of these huge price increases in those instances.

Have we reached that level?

Mr. BERRYMAN. I think we are approaching that level. I would say to you that we would already have approached it, had not the third parties been paying for the products all along. The consuming public would have refused to pay for the "me-too" products, because prices would have been too great.

The CHAIRMAN. Ultimately, does not the consuming public pretty well pay for everything?

Mr. BERRYMAN. Yes, sir, but it is hidden.

The CHAIRMAN. All right.

Dr. Wilkins, I wonder if you or Dr. Schmidt would have a quick response to my basic question there about getting all the manufacturers together in this room?

Dr. WILKINS. My comment would be that before you can negotiate with the drug companies, you have to build a system first. To my knowledge, that has not been built. You need a system where you have a clinical program, a policy structure and so forth that would allow you to be a negotiator. I certainly would recommend that you sit down with those drug companies, but I don't know that you are really in a position at this point to bargain.

The CHAIRMAN. Dr. Schmidt.

Dr. SCHMIDT. I would agree.

The CHAIRMAN. You would agree that we ought to sit down with them?

Dr. SCHMIDT. Yes, definitely sit down. But they need a structure on how you are going to work and manage through the whole problem, so you won't just solve it in one meeting. It's a long-term relationship.

The CHAIRMAN. I thank you, and I thank all of you.

Yes, Senator Cohen.

Senator COHEN. Mr. Berryman, I was intrigued by your answer to Senator Pryor. I think you said that we would have reached the critical mass as far as market absorption was concerned much earlier if there had not been the presence of third-party payors. Is that right?

Mr. BERRYMAN. Yes, sir.

Senator **Cohen**. So if you take that argument to its conclusion, then, it has been the intervention of the third-party payment system that has prevented a reduction in the price structure much earlier. In other words, if people had to pay their own bills, they never would have paid it, and we would not see those kinds of prices. By virtue of the third-party payment system, we have hidden the costs so that it is always somebody else paying, either through cost shifting or higher taxes spread among the people, so prescription drug consumers don't feel the immediate impact directly upon themselves.

So by the third-party payment system, we have actually increased the price escalation over the years, because everybody thought somebody else was paying for it?

Mr. **Berryman**. I believe that. As an example, whether you are a Medicaid recipient or a Blue Cross subscriber, if it costs you $1, $3, or $5 deductible to get a prescription filled, you will have a higher utilization than if you have to pay the entire bill.

Dr. **Wilkins**. Senator Cohen, can I respond to that?

I think third-party programs started because people could not afford medication. We have to remember that. An important point for all of us, especially in managed care, it is true, we have insulated the patient, the physician, and the payor from true health care costs and that's why we have to build programs like PARTNERS to ensure that awareness and responsibility for health care costs can be shared. But I don't think we should say that third-party programs cause the problem.

Senator **Cohen**. Whether or not they caused the problem, they have hidden the costs, allowing the costs to continue to escalate, because there is the assumption that somebody else is paying the bill. I would say it applies to many of our insurance programs.

In the personal injury field, for example, we have seen and witnessed the socialization of injury. We have accidents that the insurance company takes care of, and the prices continue to escalate because there is a notion that the company is paying for it. They spread the premiums out well beyond your personal risk.

You might have an excellent record, and still you are paying very high premiums, because the risk is being spread—it is being socialized such that somebody else is always paying the bill.

I am not suggesting that we do away with insurance, but the whole notion that, under these third-party payment systems, somebody else is paying when in fact we are all paying higher and higher costs—that's being taken advantage of by those who are supplying the product.

The **Chairman**. Thank you, Senator Cohen. Over there is Senator Grassley from Iowa. Do you have a comment or questions?

STATEMENT OF SENATOR CHARLES GRASSLEY

Senator **Grassley**. Senator, at this point I should not take time from the committee except to explain that I was in a markup in Judiciary, and that is my reason for not being here when you commenced the hearing.

I do have a very lengthy statement I want to put into the record.

[The prepared statement of Senator Grassley follows:]

STATEMENT OF SENATOR CHARLES E. GRASSLEY FOR A HEARING OF THE SPECIAL COMMITTEE ON AGING ON PHARMACEUTICAL DRUG PRICING, WEDNESDAY, NOVEMBER 16, 1989

MR. CHAIRMAN, AS I NOTED IN YOUR FIRST HEARING ON THE PRESCRIPTION DRUG PRICING POLICIES OF THE BRAND NAME DRUG MANUFACTURERS, IT IS CLEAR THAT A NUMBER OF CONFLICTING GOALS ARE AT ISSUE IN THIS MATTER.

I SEE NO REASON TO CHANGE MY MIND AS WE START THIS SECOND HEARING. IN MY VIEW, IT IS CLEAR THAT IT IS RISKY AND EXPENSIVE TO DEVELOP NEW DRUG ENTITIES. RELATIVELY FEW TRULY NEW PRODUCTS, OF THE GREAT MANY IN WHICH INVESTMENTS ARE MADE, MAKE IT TO THE MARKET. AFTER NEW DRUG ENTITIES DO MAKE IT TO THE MARKET THEY THEN HAVE PATENT PROTECTION FOR A RELATIVELY SHORT PERIOD OF TIME BEFORE CHEAPER GENERIC VERSIONS APPEAR IN THE MARKET.

IT ALSO SEEMS CLEAR, TO THIS SENATOR AT LEAST, THAT EFFECTIVE PHARMACEUTICALS RAISE THE QUALITY OF HEALTH CARE AVAILABLE TO THE AMERICAN PEOPLE.

THE ARGUMENT TO THE EFFECT THAT THE HIGH LEVELS OF INVESTMENT IN RESEARCH AND DEVELOPMENT IN PHARMACEUTICALS HAS LEAD, IN RECENT YEARS, ONLY TO A FLOOD OF "ME-TOO" PRODUCTS OF NO THERAPEUTIC VALUE SEEMS TO ME OVERDRAWN AND NOT CONVINCING, OR AT LEAST NOT YET CONVINCING.

THUS, SO FAR, IT SEEMS TO THIS SENATOR THAT THE CONGRESS NEEDS TO EXERCISE SOME CARE IN ANY LEGISLATIVE INITIATIVES IT UNDERTAKES THAT COULD HAVE A NEGATIVE EFFECT ON THE ABILITY OF AMERICAN PHARMACEUTICAL MANUFACTURERS TO DEVELOP NEW CHEMICAL ENTITIES.

AT THE SAME TIME, HOWEVER, THERE IS CAUSE FOR CONCERN. PHARMACEUTICAL PRICES HAVE RISEN MORE RAPIDLY THAN THE GENERAL CONSUMER PRICE INDEX.

AND THERE ALSO SEEMS TO BE NO QUESTION THAT MANY DRUG MANUFACTURERS FOLLOW A MULTI-TIERED OR SEGMENTED PRICING POLICY THAT GOES BEYOND THE BOUNDS OF WHAT COULD BE JUSTIFIED BY REASONABLE VOLUME DISCOUNTS.

SUCH MULTI-TIERED POLICIES CAN HAVE VERY ADVERSE EFFECTS ON PURCHASERS WHO DO NOT HAVE GREAT MARKET POWER:

- SUCH AS RETAIL PHARMACISTS, FROM WHOM WE HEAR A GREAT DEAL ON THIS SPECIFIC ISSUE.

- SUCH AS INDIVIDUALS DEPENDENT ON PARTICULAR LIFE MAINTAINING SOLE SOURCE MEDICATIONS. THE CHAIRMAN OF THE IOWA MYASTHENIA GRAVIS ASSOCIATION, MR. JOHN CARLSTEN, CALLED MY OFFICE YESTERDAY TO SAY HOW PLEASED HE WAS THAT THE COMMITTEE WAS HAVING THIS HEARING, AND TO DESCRIBE THE SITUATION NOW FACED BY THOSE WHO HAVE THIS DISEASE AND WHO ARE DEPENDENT ON A SMALL NUMBER OF DRUGS, PARTICULARLY, IN THIS CASE, MESTINON.

THE SUBSTANTIAL AND REGULAR PRICE INCREASES IN THESE PRODUCTS, WHICH I JUST MENTIONED, AGGRAVATES THE DIFFICULTIES FOR SUCH PARTIES.

AT LEAST ONE MAJOR PHARMACEUTICAL MANUFACTURER HAS TOLD MY STAFF THAT THEY HAVE AN "EQUAL ACCESS" POLICY FOR ALL OF THEIR CUSTOMERS, WITH THE EXCEPTION OF THE VETERANS ADMINISTRATION, FOR ALL OF THEIR PRODUCTS. THE V.A. EXCEPTION, THEY ARGUE, IS JUSTIFIED ON THE GROUNDS OF THE GREATER VOLUME THE V.A. IS ABLE TO PURCHASE.

THE QUESTION WHICH ARISES, OF COURSE, IS THAT IF ONE WELL-KNOWN, INNOVATIVE MANUFACTURER CAN FOLLOW AN "EQUAL ACCESS" PRICING POLICY, WHY CANNOT OTHER MANUFACTURERS?

I THINK WE ALSO HAVE A RIGHT TO KNOW WHY THE FEDERAL GOVERNMENT CANNOT BE A MORE INTELLIGENT PURCHASER OF PHARMACEUTICAL PRODUCTS. THIS IS A QUESTION THAT YOU HAVE ASKED, MR. CHAIRMAN, ON SEVERAL OCCASIONS, AND IT IS A QUESTION WHICH I BELIEVE WE SHOULD ASK. IN FACT, IT IS A QUESTION THAT WE HAVE THE RESPONSIBLITY TO ASK.

AND I THINK WE ALSO HAVE THE RESPONSIBILITY TO TRY TO MAKE SURE THAT FEDERAL MONEY IS BETTER SPENT IN THIS AREA.

AS YOU KNOW, FOR SOME YEARS I HAVE BEEN VERY UNHAPPY WITH THE WAY IN WHICH THE DEPARTMENT OF DEFENSE PURCHASES WEAPONS SYSTEMS. CLEARLY, THERE ARE DIFFERENCES BETWEEN MAKING DRUGS AND PURCHASING WEAPONS. NEVERTHELESS, IT SEEMS TO ME PERFECTLY APPROPRIATE TO INSIST THAT THE FEDERAL GOVERNMENT USE THE FEDERAL TAXPAYERS' MONEY TO GET THE BEST POSSIBLE PRODUCT FOR THE LEAST MONEY, AND WE DO NOT APPEAR TO BE DOING THAT AT PRESENT.

I THINK I HAVE TAKEN ENOUGH TIME FOR THE MOMENT, MR. CHAIRMAN. I LOOK FORWARD TO LEARNING MORE FROM OUR WITNESSES.

The **CHAIRMAN**. It looks very lengthy from here.

We are going to keep the record open for a few days, Senator Grassley. You have been a long and faithful member of this committee, and we appreciate your joining us at this time. We have had some very constructive witnesses, and some very telling testimony.

Let me advise Senator Grassley and those of you who may have gotten in later. At 1:30 this afternoon we will reassemble, as many of us who desire to in this room.

We are not through. We have another fascinating panel here. This afternoon's session will be an informal discussion where we will all sit together and talk about some of these problems and see if we can come together with a mutuality of understanding and interests that hopefully can be implemented into a positive action later. That will be at 1:30 p.m.

We will now excuse the panel, and we thank you very, very much.

We will call our next panel. We have never had any international witnesses before the Committee in the past that I am aware of. Mr. Guido Adriaenssens, and Mr. Guido Sermeus, I would like to say that we extend on behalf of this committee a very, very warm welcome to each of you. You are from Brussels, Belgium, and are highly respected for your research on international drug price comparisons. In our earlier hearing, we talked about the U.S. consumer paying the highest drug prices of anyone in the world, and the cost of prescription drugs.

I think it would a safe bet to say that whatever you say is going to probably be disputed by the pharmaceutical manufacturers. What you have done is to compare the actual price the American consumer is paying with the actual price of the consumer in Europe.

For example, on U.S. prices, you have done away with the sales tax, because in many of our States, probably 40 of our States, there is no sales tax. Similarly, with respect to the European community, you have eliminated the value-added tax on the drugs under question. So, you have developed and are about to present an international drug pricing comparison that is as fair as possible, and we look forward to your statement.

STATEMENT OF GUIDO ADRIAENSSENS, BELGIAN CONSUMER ASSOCIATION, BRUSSELS, BELGIUM

Mr. **ADRIAENSSENS**. Thank you for giving us the opportunity to give this interesting comparison between U.S. and European prices for prescription drugs.

The comparison took us a long time, but the flights to New York took even longer. It only took 25 hours.

I will not get into the methodological details at this moment. I will go straight to the results.

We have made a comparison of 25 products, considered to be a representative for consumption as well in the United States as for Europe. Of course, if we could add more data, it would be useful, but we don't think it would change anything essential to this point.

You told me that perhaps we will have discussions with industry on this comparison. But from the other side, I think there will be not so much discussions because the method we used is in fact one which favors the U.S. industry.

If we look at those 25 products we compared, a number of times, the United States has the highest prices compared to those in Europe. I will give you one example. A common tranquilizer, Valium, which is 10 times the price in Greece, for example.

The **CHAIRMAN**. Excuse me. Do you mean a U.S. citizen pays ten times the price for Valium that you would pay in Greece?

Mr. **ADRIAENSSENS**. Indeed. The average U.S. price is ten times the price a consumer would pay in Greece. The highest U.S. prices are 15 times the prices in Greece.

Let me go back to the graph, if you can see this. That graph gives the price index for the total basket of 25 products in each country, when compared to the cheapest country, which we have given index 100, that is Greece. Or if you want to have another comparison which gives in fact the same details, but perhaps in another way, we have compared the total price for these basket of 25 products with the European Economic Community average. We will see that the average prices in the United States are 54 percent more expensive than the average prices in the European Economic Community.

You can also see from this graph that the prices in the United States on average are close to those in Germany and the Netherlands. But I will come back to that point later. The next table gives you a comparison between prices in those countries who have a strict price control system, and those countries who have no price control system.

The third group consists of Ireland and the United Kingdom, which has a little bit different system. We can come back to that later also.

I told you that the prices in the United Kingdom seems to be like those available in Germany or in the Netherlands, but one should also take into account some other elements.

First of all, are patients paying for the drugs they have been prescribed or is there a reimbursement system and how favorable is this reimbursement system? We have made a comparison for the EEC. Patients in the EEC normally pay between 12 percent, in Germany, and 56 percent, in Denmark.

The elderly pay in general less or nothing at all.

A second point of interest is, is the consumption of drugs high? We would like to present two indicators in this respect. First of all, the per capita consumption, and second the percentage of the GNP spent on pharmaceutical products.

In both comparisons the United States scores very high and comparable with Germany. Germany indeed combines, as does the United States, high prices with high consumption. Recently, Germany has taken measures to reduce this high consumption pattern and also to reduce prices of drugs, because the situation becomes unbearable for the national health insurance.

As a general conclusion based on these preliminary data, we can say that the prices for prescription drugs in the United States are very high. They are comparable to the most expensive countries in

Europe (the Netherlands and Germany), but in the Netherlands the consumption of drugs is very low, not even half the consumption of the United States, and in Germany the patients, as in the Netherlands, pay only a very small contribution per prescription.

To give you an idea, in Germany, a patient would pay $1 per prescription, whatever the price of it would be.

The **CHAIRMAN**. Let me stop you there. The patient would pay $1 per prescription in Germany.

Mr. **ADRIAENSSENS**. Yes, indeed.

The **CHAIRMAN**. But the price of the drug itself is still according to the charts, much lower than the cost of the drug in the United States, is that correct?

Mr. **ADRIAENSSENS**. It will depend on the number and kind of the drug, but in general, the price in the United States is higher.

The **CHAIRMAN**. It is higher in the United States?

Mr. **ADRIAENSSENS**. Yes.

The **CHAIRMAN**. Thank you.

Mr. **ADRIAENSSENS**. So in fact, a system in which pharmaceutical companies can set prices as they wish and in which the consumer, which is the patient, or the State, or the insurance company, cannot tackle these prices with normal market mechanisms, as shopping around for the best dealer quality price comparison. It seems to us very unfair.

[The prepared statement of Mr. Adriaenssens follows:]

Association
Belge des
Consommateurs
Association Sans But Lucratif

STATEMENT PREPARED FOR THE UNITED STATES SENATE SPECIAL COMMITTEE ON AGING.

ORAL TESTIMONY - WASHINGTON DC - NOVEMBER 16, 1989.

PART I : INTERNATIONAL PRICE COMPARISON BY G. ADRIAENSSENS

The Belgian Consumers' Association, which is an independent institute for comparative testing and surveys, has been carrying out several price comparisons on pharmaceutical products for the Directorate-General for Consumer Affairs of the European Commission.
We have now been asked by this Special Committee on Aging whether it was possible to compare prices of drugs between Europe and the U.S.A.
The best way to make such a comparison is to compare all the products which are as well available in all countries of Europe and which are also in the U.S.A. available. One should also compare all package sizes, forms and strengths available. Such a study would take several years of work and enormous amounts of work.
As this is not possible we have tried to make samples which are good indicators for the general price level of pharmaceutical products.
The sample of products we used in the EEC-studies is composed of 125 products.
This list is composed of the top selling products in each of the EEC-Memberstates and represents at least 20 % of sales by value in each country.
From tabulations of the PDS Senior Scripts Data provided by the Senate Special Committee on Aging, we have been able to abstract 25 perfect matches.
So, we have made a price comparison for those 25 products. If more data become available (prices for other strengths, package sizes, etc.) we will be glad to incorporate them if the Committee thinks this would be useful.

This would of course strengthen the comparison but based on our experience we can say that it will not change the results we found until know in a dramatic way. Let's have a look at our preliminary results.
Table 1 is a listing of the 25 products with each time the country with the lowest and the country with the highest price. The U.S.A. is never the cheapest and 4 times the most expensive, when we take in account the average US-prices. It would be many times the most expensive if we take the highest prices charged is the U.S.A. for each particular drug.

Indeed the 1 % most expensive prices charged for each of the 25 drugs are in average 35 % more expensive than the average retail prices. If we would not take into account the VAT, which is applicable on drugs in most European countries, then the U.S.A. would be the most expensive in at least 7 cases.
Table 2 (and the graph) gives the price index for the total basket of 25 products in each country (without VAT) when compared with the cheapest country (= index 100) and compared with the EEC average (= index 100).
Average prices in the U.S.A. are 54 % more expensive than average prices in the EEC.
The US average prices are comparable to the extreme high prices which are found in Germany and the Netherlands.
In table 3 we have brought together some countries : those with a strict price control system for pharmaceutical products, those with no price control at all on pharmaceutical products, and the UK and Ireland as a third group because they have a different system which is in between the 2 previous groups.

We have now looked at general price levels for drugs but when comparing prices one should also take in account some other elements :
- Are patients paying the drugs they have been prescribed or is there a reimbursement system and how favourable is this for the patient ? Table 4 gives the results we found in our 125 product comparison for the EEC. Patients pay normally between 12 % (Germany) and 56 % (Denmark). The elderly pay in general less or nothing at all.

- Is there a high consumption in drugs ? We would like to present two indicators in this respect : first of all the pro capita consumption and secondly the percentage of the GNP spent on pharmaceutical products (table 5).
In both comparisons the U.S.A. scores very high and comparable with Germany. Germany combines (and we think the U.S.A. also) high prices with high consumption. Recently Germany has taken measures to reduce this consumption pattern and also to reduce prices of drugs, because the situation becomes unbearable for the national health insurances.

As a general conclusion based on these preliminary data we can say that the prices for prescription drugs in the U.S.A. are very high. They are comparable to the most expensive countries in Europe : the Netherlands and Germany, but in the Netherlands the consumption of drugs is very low (not even half the U.S.A. pro capita consumption) and in Germany the patients pay only a very small contribution per prescription (2 DM) or less than 1 US dollar).

TABLE 1

LIST OF PRODUCTS INCLUDED IN THE COMPARISON AND THE MINIMUM AND MAXIMUM PRICES IN US DOLLARS

NAME OF DRUG	AVERAGE PRICE	MINIMUM PRICE		MAXIMUM PRICE		AVERAGE USA PRICE
		VALUE	COUNTRY	VALUE	COUNTRY	
VIBRAMICINE	15,2	4,3	Greece	30,9	Germany	23,3
SECTRAL	20,8	6,4	Italy	27,6	U.K.	21,7
MODURETIC	9,8	4,3	Greece	18,1	Germany	12,4
RUFEN	7,4	4,0	Greece	16,1	Germany	4,4
SEPTRA	7,1	2,8	Spain	12,9	Germany	10,9
LASIX	4,5	1,9	Greece	9,6	Netherlands	3,6
DALMANE	8,2	2,4	Portugal	13,8	Denmark	13,0
VALIUM	3,6	0,9	Greece	9,7	USA	9,7
TECROTOL	10,5	5,8	Portugal	16,5	Germany	15,4
DIABETA	7,5	2,3	Spain	15,7	Netherlands	11,0
LOPRESSOR	19,8	8,1	Spain	36,6	Denmark	34,1
ADALAT	16,2	7,4	Spain	29,7	Denmark	19,3
ZANTAC	29,7	16,4	Greece	45,4	Germany	13,4 **
ALDOMET	18,0	8,6	Spain	32,4	Denmark	25,3
MICRONASE	7,1	2,3	Spain	15,7	Netherlands	11,6
ISOPTIN	7,7	3,1	Spain	13,2	Netherlands	9,1
DYAZIDE	8,4	2,7	Italy	16,1	Netherlands	11,3
CAPOTEN	27,9	12,5	Greece	41,8	Ireland	21,5
CARDIZEM	23,5	12,7	Italy	32,5	Spain	27,5
CECLOR	14,5	8,1	Spain	20,7	Germany	16,3
NITRODISK	41,1	23,8	Greece	68,0	Ireland	35,6
LOZOL	13,6	5,4	Spain	21,6	Denmark	15,4
HALCION	6,3	3,1	Portugal	14,6	USA	14,6
XANAX	16,5	6,9	France	37,5	USA	37,5
CLINORIL	62,4	32,7	Portugal	87,7	USA	87,7

** Subsequent to the hearing of 11/16/89, this figure was corrected by the witness. The correct price for an equivalent package should have been stated as $22.94. The graphs and tables reflecting relative cost of products in the U.S. and EC have not been adjusted to take this change into account.

TABLE 2

Index for prescription drugs based on a sample of 25 products (1988) *		
Country	Cheapest = 100	EEC average = 100
Greece	100	55
Spain	105	58
Portugal	116	64
France	127	70
Italy	131	72
Belgium	166	92
United Kingdom	217	120
Ireland	228	126
Denmark	230	127
Germany	269	149
Netherlands	299	165
EEC-average	181	100
United States of America	279	154

* calculations based on weighted retail prices without VAT

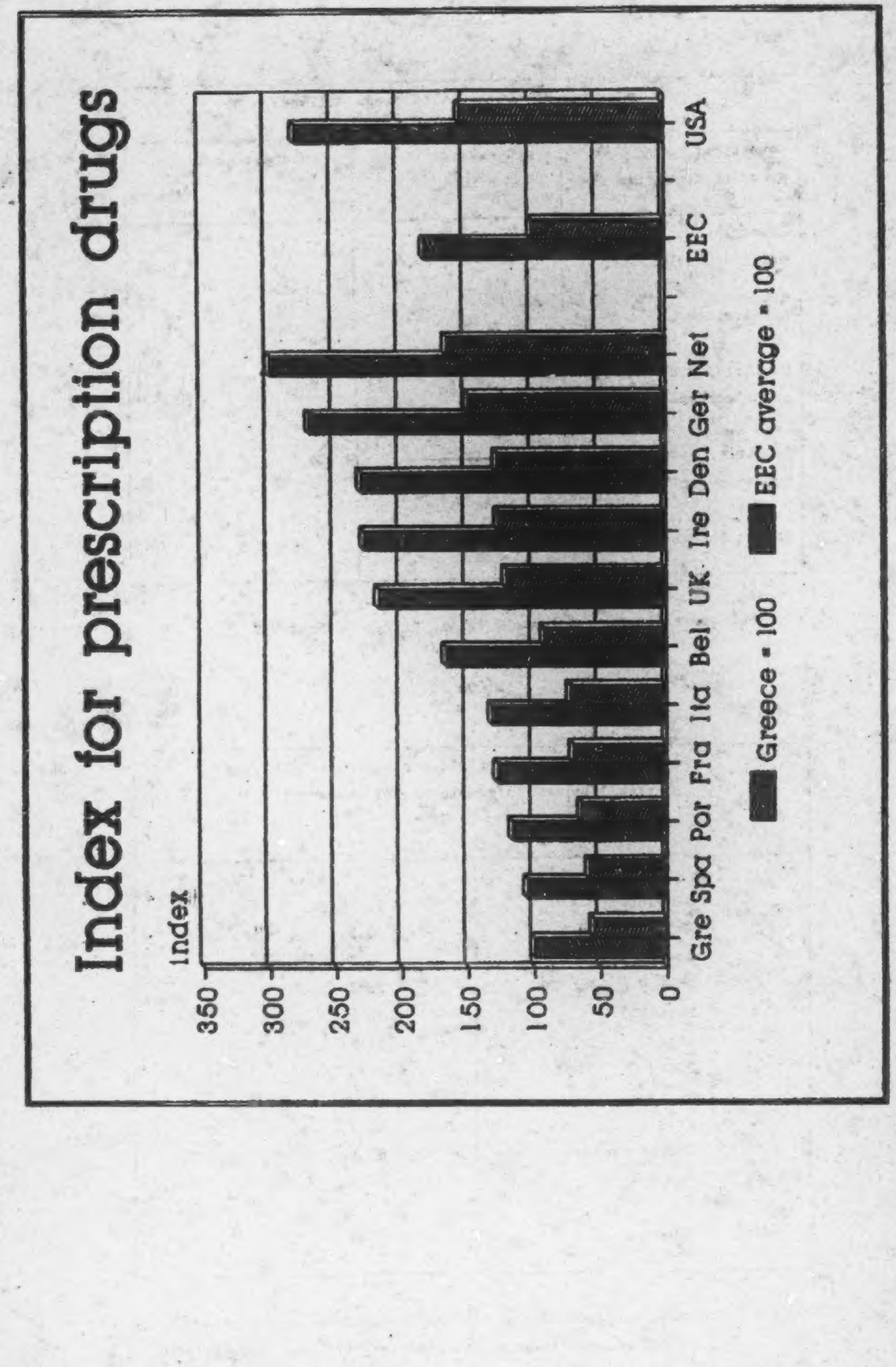
Index for prescription drugs
Index
350
300
250
200
150
100
50
0
Gre
Spa
Por
Fra
Ita
Bel
UK
Ire
Den
Ger
Net
EEC
USA
Greece = 100
EEC average = 100

TABLE 3

Index for 25 prescription drugs * (1988)		
Country or group of countries	EEC average = 100	cheapest group = 100
Countries with strict price control system	68	100
EEC-average	100	147
Countries with limited price control system	123	180
Countries without price control system	147	216
United States of America	154	226

* calculations based on weighteid retail prices without VAT

TABLE 4

Average % of the patient's contribution to the drug retail price (in sample of 125 products)	
Germany	12 %
Netherlands	13 %
Luxemburg	18 %
Greece	26 %
Portugal	32 %
Italy	33 %
Spain	35 %
Belgium	42 %
France	43 %
United Kingdom	52 %
Denmark	56 %
EEC-Average	33 %

Note : In most countries there are many exceptions to the general rules of reimbursement. The disabled, orphans, widows, etc. can often have free dispening. In the UK, for exemple, it is estimated that 60 % of all NHS supplies are free.

TABLE 5

Pro capita expenditure on pharmaceutical products and percentage of GNP spent on pharmaceutical products (1988)

Country	pro capita expenditure EEC-average = 100	total pharmaceutical expenditure as % of GNP
Italy	98	1.341
France	124	1.440
Germany	150	1.487
United Kingdom	63	0.884
Belgium	88	1.146
Netherlands	63	0.811
Spain	56	1.299
EEC-Average	100	1.361
USA	152	1.485

Calculations based on and figures from Indicatori Farmaceutici 1989, Farmindustria.

The **Chairman**. Thank you very much. We used a chart in our last hearing,[6] the one in green, to our far left here. This was done by an Italian pharmaceutical manufacturer organization. Do you see any discrepancy in that chart and the chart that the two of you drew up, or the conclusions that you reached here? Are we running about the same?

Mr. **Adriaenssens**. I don't think there is any difference between the two charts. Perhaps the figures are different, but that is only due to the methodology. Affecting the first comparison, one compares all packages in whatever country they are available. While in our comparison, we only compared the same packages, packages which are available in the United States as well as in European countries.

In this comparison for example, the Italian comparison, a normal package in Italy would only have 20 tablets in it, while in the United States a normal package can be 100 tablets. So I think there is a difference in methodology, but as you will, the ranking of countries is almost the same.

The **Chairman**. In your methodology, you used 100 tablets for 100 tablets in your comparison.

Mr. **Adriaenssens**. Yes. I think our comparison is more favorable for the U.S. industry.

The **Chairman**. I see. We appreciate you being factual with us. We are trying to get to the bottom of the facts. I failed to mention in my introduction of my two distinguished guests that they both represent the Belgian Consumer Association and biographical information on both of these witnesses this morning will be available upon request.

They are highly respected throughout Europe for their published studies on international drug price comparisons, and I know this is a very unique and difficult area to work in. I doubt there are very many people like you in the world who do this, who compare drug prices.

Let me ask this about the European manufacturer. Does the government or does the individual citizen have access to what you might say proprietary interests of the manufacturer? Does the government know about some of the proprietary interests the manufacturer might own?

Mr. **Adriaenssens**. I am not sure I understand your question.

The **Chairman**. Does the government, in dealing with or in purchasing prescription drugs, does the government use facts that perhaps we do not use in the Congress in determining the ultimate price to pay the manufacturer for the drugs?

Mr. **Adriaenssens**. Yes, indeed. In many countries in the EEC, the governments decide on the price which seems fair to them, and not the reverse. So in fact, government in all those countries, like Spain, France, Italy, Belgium, also, the government is setting the price of the pharmaceutical products.

The industry can make a suggestion, and explain how they come to the price they propose, but in fact, the government fixes the price for that drug which seems comparable with other drugs which have about the same ingredients or the same effect.

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[6] See appendix 1, p. 339.

The **Chairman**. Does the government in the European countries that we see here on your chart, do they negotiate or set a limit on the profits the manufacturer may make?

Mr. **Adriaenssens**. Yes. The group of countries, the U.K. and Ireland, for example, have a system in which they do not fix the price of one particular drug, but they fix the profit of a company. Then the industry can choose themselves which drugs they are going to raise in price, or not.

The **Chairman**. In this regard, does the government in establishing this price, is there any sort of an incentive paid by the government to the pharmaceutical manufacturers, for research and development? Do you have any sort of an incentive for research and development for the manufacturer?

Mr. **Adriaenssens**. I think that every government takes into account the insurance of whatever company, not only for pharmaceutical companies. They allow reasonable profits, so that they can be sure that the companies can introduce new research and pay for the new research.

Because one of the issues in these discussion is often that there should be a strong pharmaceutical industry to counter the American industry on pharmaceuticals.

The **Chairman**. Are American drugs being manufactured in America by American manufacturers being sold today in these European countries at a lower price than the American consumer is buying that drug? I am not talking about products from European drug manufacturers, I am talking about products made in America. Are they sold in Europe cheaper?

Mr. **Adriaenssens**. Yes, in most cases, I think. Over 50 percent cheaper than in the United States. The average price in Europe is 50 percent cheaper.

The **Chairman**. I assume, and I hope that you had the opportunity to listen to some of the previous witnesses sitting at the witness table.

Did you happen to hear the gentleman from New York when he was talking about members of that community that he represents having to get drugs from Europe to sustain their lives? Was that a surprise to you, or was that a revelation? Or is this something accepted and acknowledged in the European market?

Mr. **Adriaenssens**. I think it is known in general that U.S. prices are high, and the inverse, that drugs are cheaper in Europe. So it is always a good deal if someone can buy a drug in Europe rather than in the United States.

The **Chairman**. We have about 20 to 25 major manufacturers. I would call those the major ones, there may be many more, and I hope I am not misstating that. But they are the larger manufacturers. How would you compare the profits of the American pharmaceutical to the manufacturer of pharmaceutical products in Europe? Are our profits to the companies higher, or lower?

Mr. **Adriaenssens**. It's a problem which is hard to discuss, because it is not always clear what the profits are on pharmaceutical products. There is a lot of transfer pricing. To give you an example, a drug can be produced in the United States, exported to Belgium, and from Belgium exported to France. Then it can be re-imported to the United States. In each step the price can become higher.

The CHAIRMAN. Let me ask this question. We talked about one particular drug. This is the drug Eldepryl. This is the drug used by Mrs. Bivens, discovered in 1964 in Hungary. An American fund may buy this drug, this pill is sold in Italy for 41 cents a capsule, $1 in Canada and $2.38 in the United States. Mrs. Bivens pays five times the amount they would pay in Italy. Why the great disparity of price differential?

Mr. ADRIAENSSENS. The most important explanation is that in the U.S. prices can be set as wished by the pharmaceutical industry, and we can perhaps talk about how they do that. In Italy, on the other side, the price is decided on objective facts which have to be submitted by the pharmaceutical industry to the government. The government decides on whether the figures they have are fair or not.

The CHAIRMAN. Does the average American consumer spend more or less than the European for prescription drugs.

Mr. ADRIAENSSENS. He spends clearly more.

The CHAIRMAN. Do we use more or less than the average European?

Mr. ADRIAENSSENS. The consumption is higher, yes. U.S. patients have a higher consumption as well in price as in number of tablets.

The CHAIRMAN. Are we the highest in the world in consumption that you know of? Do you have a figure on that?

Mr. ADRIAENSSENS. Yes. I don't think your prices are the highest. As you have been several times in the past, you are beaten by the Japanese.

The CHAIRMAN. By the Japanese? Okay. Let's look for a moment at the Netherlands. They are the only ones on the chart that seem to be paying a higher price than Americans. Why is that? What has happened in the Netherlands?

Mr. ADRIAENSSENS. In the Netherlands, the prices are very high, they have a very free system. The patient doesn't bother because they are all reimbursed. They all pay something around $1 for each prescription. And the consumption in the Netherlands is very low.

So if you look at the expenditure per person, or patient, in the Netherlands, the total expenditure is only half of the expenditure of an average U.S. citizen.

The CHAIRMAN. If you came over—I know you did not cross the Atlantic, and I hate that the flight took so long, 25 hours—if you came over to give us advice, although I know you are here to state facts, would you advise us if it might be time for us to negotiate as a government with the manufacturers of our prescription drugs and try to get a better price?

Mr. ADRIAENSSENS. Yes. I think in every free market there is a purchaser and someone who produces the products. The negotiation also comes from both sides. It seems unfair to have a system in which only the producer can fix prices, and the patient or purchaser cannot negotiate. The purchaser can be the patients or the government or the insurance company.

The CHAIRMAN. You are stating—once again, I want to get this figure right—we have excluded the sales taxes, value added taxes, there is about a 54-percent increase in drug prices over that or higher cost paid by the consumer than the average European country, is this correct?

Mr. ADRIAENSSENS. Yes.

The CHAIRMAN. The price controls in the European companies, have they helped? What has been the effect of price controls in the European countries?

Mr. ADRIAENSSENS. Perhaps my colleague can explain this.

The CHAIRMAN. Certainly.

Mr. Sermeus.

STATEMENT OF GUIDO SERMEUS, BELGIAN CONSUMERS ASSOCIATION

Mr. SERMEUS. Perhaps I can give you four different ways which are used in Europe to try to control expenses for drugs. I have to say first, that in general the main argument from the pharmaceutical industry is that by using those mechanisms the government is destroying free market competition which is, as has already been discussed here, complete nonsense.

Because the basic conditions for a free market mechanism are not fulfilled. Doctors are prescribing those drugs, but they don't have to pay for it. Patients are consuming them but they only have to pay a small part of it. Several studies in Europe show that the doctors or practitioners are not even aware of the price of the drugs.

The only thing they know, and that's very important, since in Europe, which is different from the United States, almost all of the citizens, not only lower income groups, but almost all of them, are covered by social insurance systems which pay for medical care and also for drug reimbursement, is whether a drug is reimbursed by the social security system or not.

In general, a doctor will try to prescribe drugs for his patients which are reimbursed. That's very important. Because that's the first way to try to control drug prices.

There are different categories of drugs being reimbursed in our social security systems, and most all of the countries have different categories. One of them is called vital drugs. For that kind of drug, there is not even a negotiation between the pharmaceutical industries and government, because those drugs are being reimbursed and the government, or the social security system, who pays for those drugs, will accept a certain price or even determines the price.

Another possibility for less vital drugs is that the government or the State gives the choice to the pharmaceutical companies whether they can lower their prices and put it in the reimbursement system or whether they can increase the prices resulting that the social system will not pay for those drugs.

Then it is up to the industry to make the balance, whether they can ask high prices and have a small volume, or whether it is more equitable that they have lower prices with high volume. In that case doctors will prescribe more of those drugs.

That's one very important thing, because setting the prices of drugs and reimbursing the drugs were two different topics. More and more in all the 12 member States of the community at the moment, there is an interference because the reimbursement system seems to be a very effective controlling system for putting the prices down. The pharmaceutical industry knows that very well.

A second mechanism that becomes used is trying to control the prescription behavior of the doctors, by informing them in different ways, and also by making profiles of their prescription behavior. If a certain group of doctors who have basically the same kind of patients with the same kind of diseases are on the top level of economic aspects as far as direct reimbursement is concerned, they have to justify it.

It goes even so far in certain countries that they can be sanctioned. The sanction can be that they are put out of the social reimbursement system, and that's very effective, because a patient knows if a doctor does not belong to the system, since the patient will then have to pay 100 percent for the prescription. That's very important.

A third way to control prices is giving the pharmacists the right of making a substitution on the prescribed drugs. Of course, that is very controversial, because here the pharmaceutical industries and the doctors are aware that they are not free to use their therapeutical freedom as they want to do.

Of course, in our opinion, it is just a question of information, because if there are equivalent drugs which are as safe and effective as more expensive ones, there is no reason to try to use that method to control drug prices. For instance in Germany this is important, since in Germany as well as in the Netherlands, the prices are very high. Our comparison is based on prices from January this year, but by that time, everything evolved very quickly. By controlling the prescription behavior of the doctors, also in Germany now, and by giving more and more rights to the pharmacists to substitute the prescriptions, they are trying to put the prices down also.

So it is very possible that at this moment, if we were to redo the comparison, the prices for Germany and the Netherlands would be lower, so that the difference between the United States and those most expensive European countries is much higher. That might be very possible.

The **Chairman**. I do apologize. I have reached a point that in about 1 or 2 minutes I will have to leave. If you would conclude your statement, I would appreciate it. Any other follow-on you would like to have placed in the record, this certainly will be placed in the record at the appropriate place.

Mr. **Sermeus**. I will conclude with the fourth way of trying to control prices. That's what has been called here the use of formularies, what we call positive and negative lists. Positive lists may have the effect of stimulating doctors to prescribe those drugs. Negative lists are really drugs which are not becoming reimbursed anymore. Those lists are sent to all practitioners.

I think those are the four most important ways to control pricing mechanisms in Europe.

[The prepared statement of Mr. Sermeus follows:]

**Association
Belge des
Consommateurs**
Association Sans But Lucratif

STATEMENT PREPARED FOR THE UNITED STATES SENATE SPECIAL COMMITTEE ON AGING.

Oral testimony - Washington D.C. - November 16, 1989.

Part II: Some general trends related to drug prices and drug reimbursement in Europe - by G. Sermeus

1. The pricing of drugs

The pricing of drugs as practised within the E.E.C. member countries is very characteristic for each individual country. This means that the pricing structure of no one country is identical to that of another country. There is no doubt that this is related to the fact that a great many variables as well as a wide range of specific conditions must be taken into consideration for the determination of prices. It would therefore not be possible to discuss and compare the complete pricing mechanism for each country on an idividual basis. Even a limited comparison based on global trends would be inappropriate since one same country can be subject to different trends according to a wide possible range of specific conditions. The following may be interpreted as a theoretical framework of pricing mechanisms.

1.1. manufacturer's price

- 1.1.1. determination of manufacturer's price
  - 1.1.1.1. price controlled by law
  - 1.1.1.2. government approves price proposed by private intiative
  - 1.1.1.3. no governmental control
- 1.1.2. future increases in manufacturer's price
  - 1.1.2.1. with basic governmental interference
    - 1.1.2.1.1. no governmental control
    - 1.1.2.1.2. governmental control
  - 1.1.2.2. without basic governmental interference
    - 1.1.2.2.1. no governmental control
    - 1.1.2.2.2. governmental control

ABC (Test-Achats) Rue de Hollande, 13 - 1060 Bruxelles - Tél. (02) 538 64 30
Société Générale de Banque [illegible] - TELEX : test 26771

1.2. wholesalers

1.2.1. governmental control of margin

1.2.1.1. yes
1.2.1.2. no

1.2.2. obligatory distribution through wholesalers

1.2.2.1. yes
1.2.2.2. no

1.2.3. margin level

1.3. pharmacists

1.3.1. governmental control of margin

1.3.1.1. yes
1.3.1.2. no

1.3.2. type of margin

1.3.2.1. percentage (fixed or variable)
1.3.2.2. other approach

1.3.3. margin level

1.4. V.A.T.

1.4.1. uniform rate applicable

1.4.2. more than one rate applicable

1.4.3. V.A.T. level

The following table locates nine of the twelve member states on their position within the above indicated scheme (situation between 1984 and 1987).

	MANUFACTURER'S PRICE							WHOLESALERS						PHARMACISTS							VALUE ADDED TAX	
	Government control over:							Government control of margin		Margin as a function of retail price		Obligatory distribution through wholesalers		Government control of margin			Margin as a function of retail price					
	Determination of manufacturer's price			future increases in manufacturer's price																		
	YES		NO	YES		NO		YES	NO			YES	NO	YES	NO						Uniform rate applicable %	More than one rate applicable %
	Price controlled by law	Government approves price proposed by private initiative		With government pricing	Without government pricing	With government pricing	Without government pricing			With government regulation	On free initiative			Percentage margin	Margin varying according to individual situation		With government regulation: % margin	With government regulation: variable margin (approximation)	On free initiative	Approximate average overall margin for more than one regulation		
BELGIUM	X			X				X		8.35% (9)		X		X			31% (18)				6%	
FRANCE	X(4)		X(1)	X	X			X		7.12%	X			X			33.46%				7%	
U. KINGDOM		X(8)	X(7)			X	X	X (11)	X (20)	12.5% (10)		X	X		X (21)	X (22)		25%	33.3%			0%(29) 15%(30)
IRELAND	X(5)		X(2)	X	X				X (13)		8.7% (14)	X (15)			X (23)	X (25)		1.231P (24)	33.3%			0%(31)-23%(32) -35%(33)
ITALY	X(6)	X(3)		X					X (16)	8%			X	X			25%				8%	
THE NETHERLANDS			X		X				X (17)		10-15%	X			X (26)					36%		5%(34) 19%(35)
WEST GERMANY			X				X	X	X (19)	8.24-10.33% (12)		X		X (27)		X (28)	23.1% 40.5%				14%	
SPAIN	X		X (36)	X				X		8.53%		X		X			28.9%				6%	
PORTUGAL	X		X (37)	X				X		10%		X (38)		X			20% (39)				0%	

Explanations : see next page.

Schematic representation of the drug pricing mechanisms

(1) for non-reimbursable proprietary medicinal products

(2) for own domestic pharmaceutical production

(3) for OTC proprietary medicinal products

(4) for reimbursable proprietary medicinal products

(5) for imported drugs by means of a control on the import margin of 7.5%.

(6) for ethical drugs

(7) for OTC drugs including those on the General Sales List, and drugs supplied privately in private practice or hospital.

(8) for drugs supplied within the N.H.S., Government control is based on the V.P.R.S. according to which the Government may intervene in the overall profit made on products supplied within the N.H.S. without, however, necessarily indicating which specific products must be subject to a price reduction.

(9) with a maximum of 73 BF per product.

(10) depending on the reimbursement received by the pharmacist within the N.H.S.

(11) for drugs supplied within the N.H.S.

(12) for pharmacy-only drugs.

(13) although there is no actual government regulation, the margin to be applied is submitted for government approval.
As a general rule, the government traditionally sets an acceptable basic margin of 15% on the manufacturer's or importer's price.

(14) this is an isolated case which is based on oral drugs supplied privately, i.e. outside the G.M.S.

(15) the most important whole-salers in Ireland also act as importers.

(16) there is no government regulation of wholesale margins. In fact the margin is determined as a result of government control of the manufacturer's price and the retail profit margin.

(17) Once the margin has been determined, then subsequent movements are subject to the provisions of the general Prices Law.

(18) with a nominal upper limit of 250 BF per item supplied

(19) with respect to freely available drugs

(20) with respect to drugs supplied outside the N.H.S.

(21) for drugs supplied within the N.H.S.

(22) for drugs supplied outside the N.H.S. and also OTC drugs

(23) for drugs supplied within the G.M.S.

(24) fixed amount per item supplied added to the actual cost price of the product as reimbursement

(25) for transactions outside the G.M.S. Although the government does not determine a margin, it does traditionally accept a margin of 50% of the wholesale price.

(26) the pharmacist's margins will vary according to whether the drugs are supplied to health insurance fund patients or private health insurance beneficiaries.

(27) with respect to pharmacy only drugs

(28) with respect to drugs available outside the pharmacy

(29) on drugs supplied within the N.H.S. and privately on prescription

(30) on OTC and General Sale list drugs

(31) on oral medicines

(32) on injections, intravenous administrations suppositories an drugs for external use

(33) on disinfectants
(34) on freely available drugs
(36) for non-authorized prices
(37) for non-reimbursable drugs
(36) for the very majority of drugs
(39) to be increased with 5% for a minority of drugs that have been directly obtained from the manufacturers or importers.

2. Conditions for the reimbursement of the cost of drugs

The greatest differences among the E.E.C. member states unquestionably occur in the conditions for the reimbursement of the cost of drugs and the reimbursement systems. Each country has its own system which has been developed historically and which has undergone changes over the years, due principally to socially motivated considerations and configurations. Such an often fundamental diversity of principles and regulations does not facilitate the drawing up of an international comparison. In order not to become lost in a maze of individual characteristics, it is necessary to restrict the comparison to some fundamental principles, and in doing so to remain aware that this may only be considered a general framework, and sometimes scarcely even that.

There are currently still differences in the systems of direct and indirect reimbursement of the cost of drugs to the patient. The term "direct" implies that the cost is borne by a third party. This means that the pharmacist will only charge his or her customer the relevant personal contribution and that for the remaining amount of the cost incurred he or she will apply directly either to the government health insurance institution or to the private health insurance company.

Sometimes, the method of reimbursement depends on the type of insurance. E.g. health insurance fund patients benefit from the system in which the third party pays the balance of the cost, whereas private health insurance beneficiaries must first pay the full price to their pharmacist and recover part of the cost incurred thereafter.

Sometimes, the patient will only receive the reimbursable proportion of the cost at the end of each calendar month on production of proof of the expenses he or she has actually incurred.

Returning to the prime motivation for reimbursement, i.e. the development of a health care system which is accessible to all strata of the population, it may be noted that such a system will vary according to the level of the material infirmity of the beneficiaries. This results in a range of subsystems within an overall system. Many regulations may today be classified according to whether they have remained as such or have been further developed and updated. These variables can therefore be used as a second discriminating factor. Such provision for subgroups within the system implies different proportional reimbursement levels of the costs incurred, ranging from a contribution which increases according to the group concerned to the completely free supply of drugs.

Another discriminating factor must be described from a historical perspective. Originally, the supply of drugs was equivalent to the supply of extemporaneous preparations by the pharmacist. Over the last few decades this concept has changed completely. Extemporaneous preparations have been completely superceded by proprietary medicinal products. These are the product of industrial research and development. Industrial activity on this front has diversified into a large number of specialist groups, with the result that a very wide range of drugs are now available. This in turn has resulted in the fact that, in most of the countries concerned, restrictions have been imposed on the reimbursement of the cost of proprietary medicinal products. Thus a limited number of drugs were selected which would be eligible for reimbursement. The most frequently recurring criteria for the selection of these drugs are prescription only drugs exclusively, qualitative improvements and improvements in terms of cost effectiveness.

The fourth and fifth factors are to be found in the way the reimbursement system has been structured and in the level of reimbursement relating to a group or category of drugs. There are actually two main systems as far as the reimbursement structure is concerned. Certain countries determine their reimbursement according to a percentage of the retail price. This means that the patient's personal contribution will increase as the price of the drug increases.
Other countries determine that a fixed amount must be paid for each item supplied.

The fifth factor has already been mentioned as the reimbursement level relating to a specific category of drugs. This system is based on a structure of qualitative interpretation used with respect to the reimbursement of the cost of drugs. The government and/or the health insurance systems divide the drugs into several categories, mainly according to criteria based on the sociomedical usefulness of the various product groups. For example, essential drugs, socially and therapeutically useful drugs, etc. As the category declines in importance, the personal contribution of the patient increases.

These five factors may be considered as the most significant determinants for the reimbursement schemes ultimately implemented. It is worthy of note that there is never any question in any of the countries concerned of a completely generalized system of free drug supplies, i.e. full reimbursement. It should also be added that, in addition to having a cost saving effect, these measures are also intended to increase awareness and promote more rational prescribing habits on the part of doctors. The modified reimbursement system does not need to be in conflict with the interests of the patient in terms of the quality and quantity of drugs prescribed, at least not if the system is to be used by those providing the health care in the most satisfactory and efficient manner.

The following table locates nine of the twelve member states on their position within the above discussed five-parameter scheme (situation between 1984 and 1987).

Schematic summary of the drug reimbursement systems

		BELGIUM	FRANCE	U.K.	IRELAND	ITALY	THE NETHERLANDS	W.-GERMANY	SPAIN	PORTUGAL
METHOD OF REIMBURSEMENT	direct reimbursement system	X		X		X		X	X	X
	mixed (direct + indirect)		X (1)		X (2)		X (3)			
SCHEME OF BENEFICIARIES	system of subcategories	X		X	X		X		X	
	uniform application of system		X			X		X		X
REIMBURSABLE DRUGS (6)	selection of products (reimbursement lists)	X	X		X (4)	X	X	X	X	X
	no selection of products (all drugs, in theory)			X (5)						
REIMBURSEMENT STRUCTURE	personal contribution = % of retail price	X (7)	X						X	X
	personal contribution = fixed amount per item supplied			X			X (8)	X		
	personal contribution = combination of % and fixed amount				X (9)	X (10)			X (11)	
REIMBURSEMENT LEVEL	according to category of drug	X	X			X			X	X
	uniform for all drugs			X	X		X	X		

Explanations : see next page.

(1) In France, the system of payment by a third party is increasingly applicable. This applies in particular to the more expensive drugs. The major obstacle to this is the resistance, on grounds of principle, on the part of the pharmacists to agree to comply wholeheartedly with this.

(2) The groups of persons who are reimbursed according to a system of excesses may be classified under the system of indirect reimbursement. Thus, this applies to reimbursements made within the Drug Refund Scheme and the Voluntary Health Insurance. In contrast to this, the persons who are reimbursed within the General Medical Service and the Long-Term Illness Scheme must be classified under the system of direct reimbursement.

(3) Health insurance fund patients are included in the system of direct reimbursement. Private health insurance beneficiaries are included under the system of indirect reimbursement.

(4) The selection which takes place in Ireland means only in fact that all OTC drugs are excluded from reimbursement. Thus no restrictions are imposed on ethical drugs, except that the cost of drugs which are assumed to be administered only under strict and constant expert supervision, i.e. in hospital, will not be reimbursed for out-patient use.

(5) All drugs which are not advertised directly to the general public are eligible for reimbursement through the N.H.S.

(6) A general condition for reimbursement which applies in all countries is that the cost of drugs will only be reimbursed if they are supplied on prescription. The persons who are entitled to issue a prescription for reimbursement are the professions authorized to issue prescriptions mentioned earlier, with the exception of veterinary surgeons since veterinary drugs are not included in the social security system.

(7) With an indication of a maximum nominal amount per product for each category of drugs.

(8) Should the fixed annual total for drugs supplied reach a specific amount, which was fixed at 125 Guilders for 1984, then no additional personal contribution is payable.

(9) The application of forms of personal contribution are found within the D.R.S. and the V.H.I. An excess is applicable within the D.R.S. which results in a contribution of a percentage of the total retail price paid by the patient per month, insofar as this monthly amount exceeds 28 Punt, and also in a fixed amount of 50 pence to be paid by the patient per prescription, irrespective of the number of items on each prescription. The V.H.I. is exclusively characterized by a reimbursement which is again a percentage of the total retail price paid by the patient during the month, applicable once the monthly total exceeds 23 Punt.

(10) Within drug category B, the patient pays a fixed amount of 1 000 lire per prescription, irrespective of the number of items up to a maximum of three items, in addition to a personal contribution of 15% of the retail price, up to a maximum of 20 000 lire per drug. In the theoretical drug category C, the patient only pays a contribution of 1 000 lire per prescription, similarly with a limit of three items per prescription.

(11) only for the reimbursed group with the highest contribution of the Social Security.

The **CHAIRMAN**. Very good. Thank you. I want to thank this distinguished panel. Our other Senators had to leave. I know that they will want to possibly ask some follow-on questions. I know Senator Grassley has questions for each of you, and those will be submitted to you by the committee.

I would like to thank both of you for being so cooperative with our staff on the Aging Committee. I would like to urge your cooperation with them in the future. You have been a great resource for us. Not only have you supplied us with valuable charts and showed us the difference in prices worldwide, but also you have supplied us drug by drug a price comparison in the respective countries compared to how the U.S. citizen as a consumer utilizes it.

So for the charts, the research, the statements, and especially your presence before this Special Committee on Aging, we are very indebted to you.

We invite all of you back—especially our panelists—to our 1:30 meeting which will be in just an hour. It will be very informal and we hope that both of you can participate. We thank all of our panelists this morning.

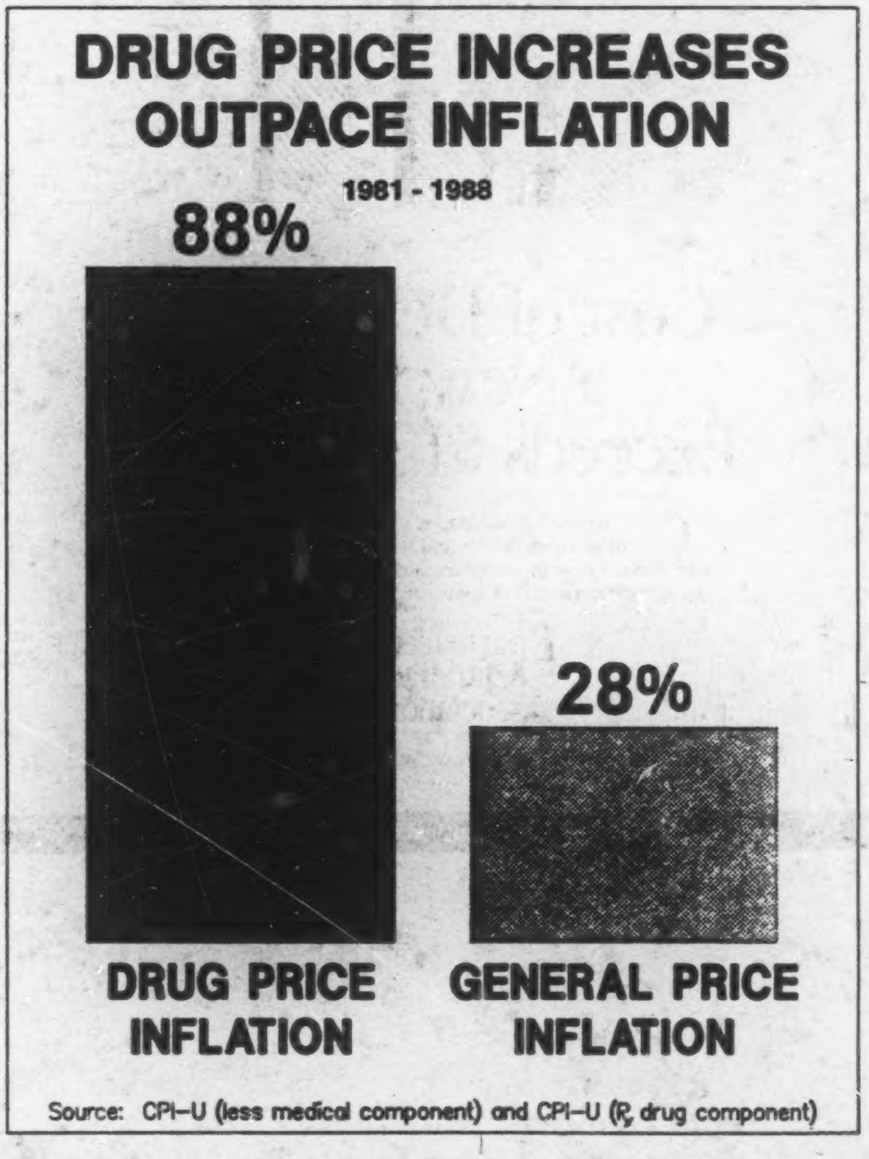
This hearing is adjourned.

[Whereupon, at 12:21 p.m., the committee was adjourned, to reconvene at the call of the Chair.]

APPENDIXES

CHARTS USED IN HEARING

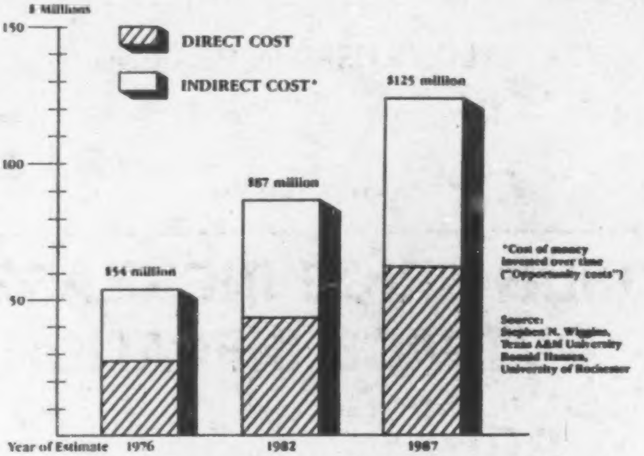
Appendix 1



Source: CPI–U (less medical component) and CPI–U (℞ drug component)

INNOVATION IN MEDICINES

#2
in a Series



*Cost of money invested over time ("Opportunity costs")

Source:
Stephen N. Wiggins,
Texas A&M University
Ronald Hansen,
University of Rochester

Cost of Developing a New Drug Exceeds $125 Million

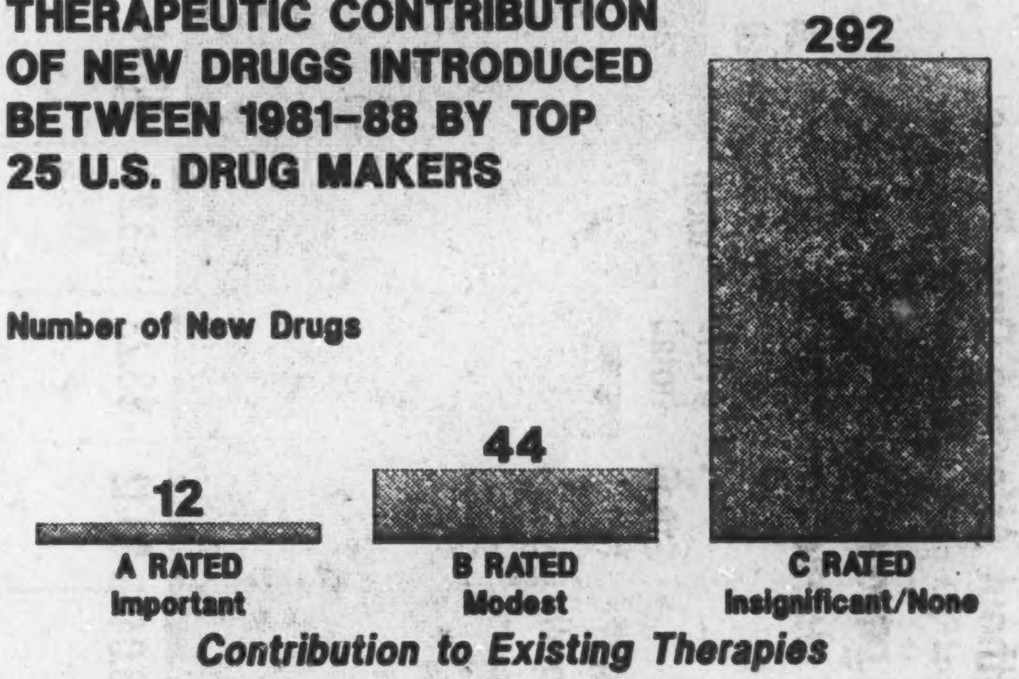
Costs are escalating because of the growing complexity of modern medicines and the 7 to 10 years necessary to move a new medicine from discovery through testing, development and FDA approval.

Pharmaceutical Manufacturers Association

1100 Fifteenth Street, N.W., Washington, D.C. 20005

America's Pharmaceutical Research Companies

THE "ME–TOO" FACTOR

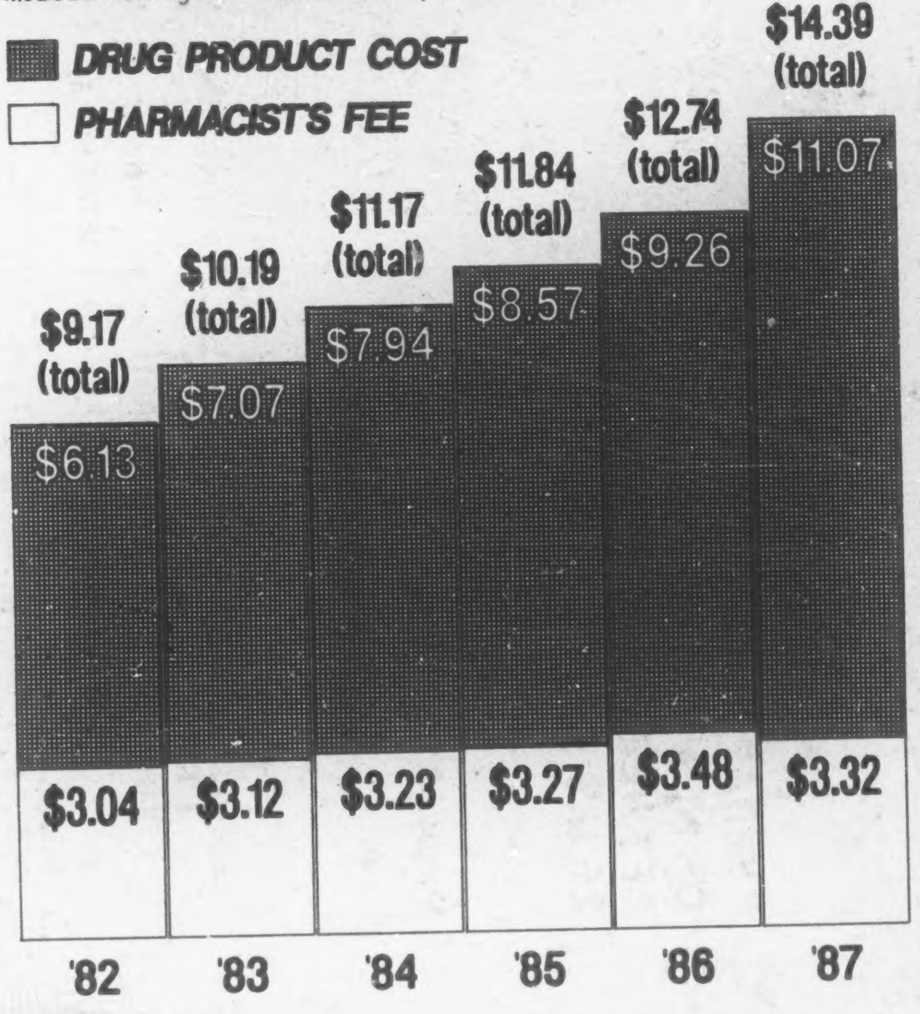


THERAPEUTIC CONTRIBUTION OF NEW DRUGS INTRODUCED BETWEEN 1981–88 BY TOP 25 U.S. DRUG MAKERS

Source: FDA New Drug Evaluation Statistical Reports, Ranking Drugs by "Therapeutic Potential"

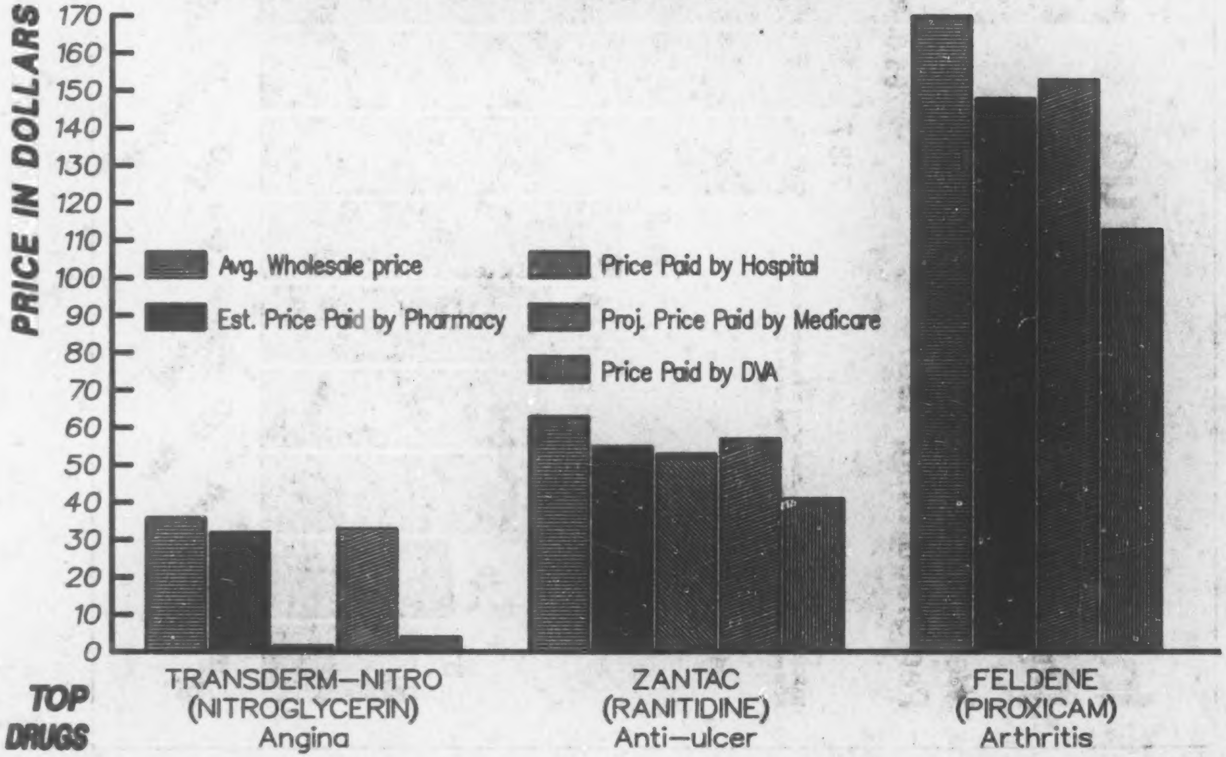
Cutting Reimbursement Hurts Pharmacies Without Affecting Drug Prices

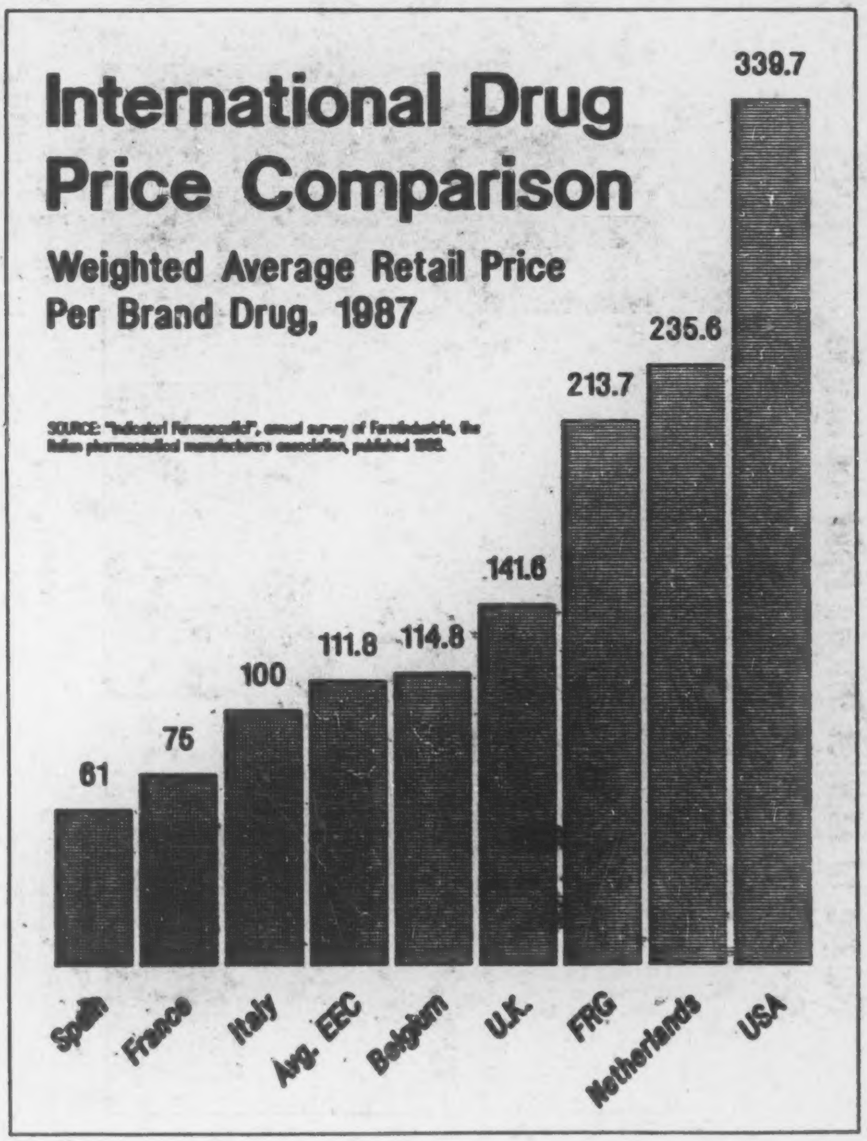
Medicaid Rx Drug Reimbursement Components, 1982–87



SOURCE: Compiled by the Pharmaceutical Economics Research Center, Purdue University, from data found in Benefits, Under State Medical Assistance Programs, Reston, VA: National Pharmaceutical Council, various years.

Range of Market Prices Paid for Single Source Prescription Drugs: Spring 1989



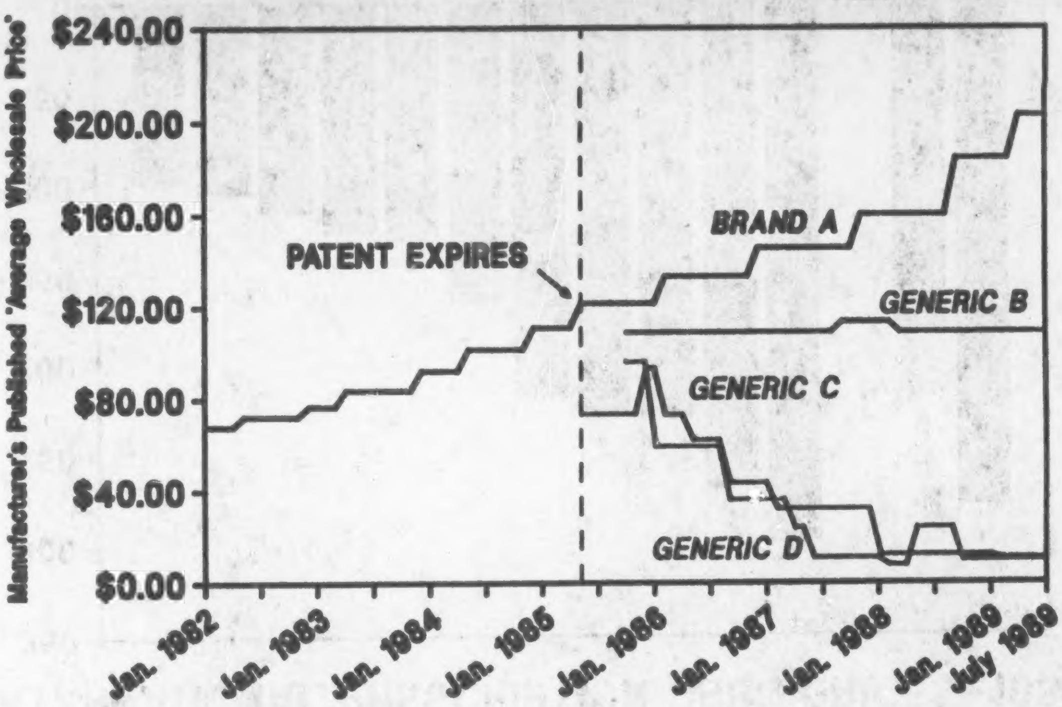


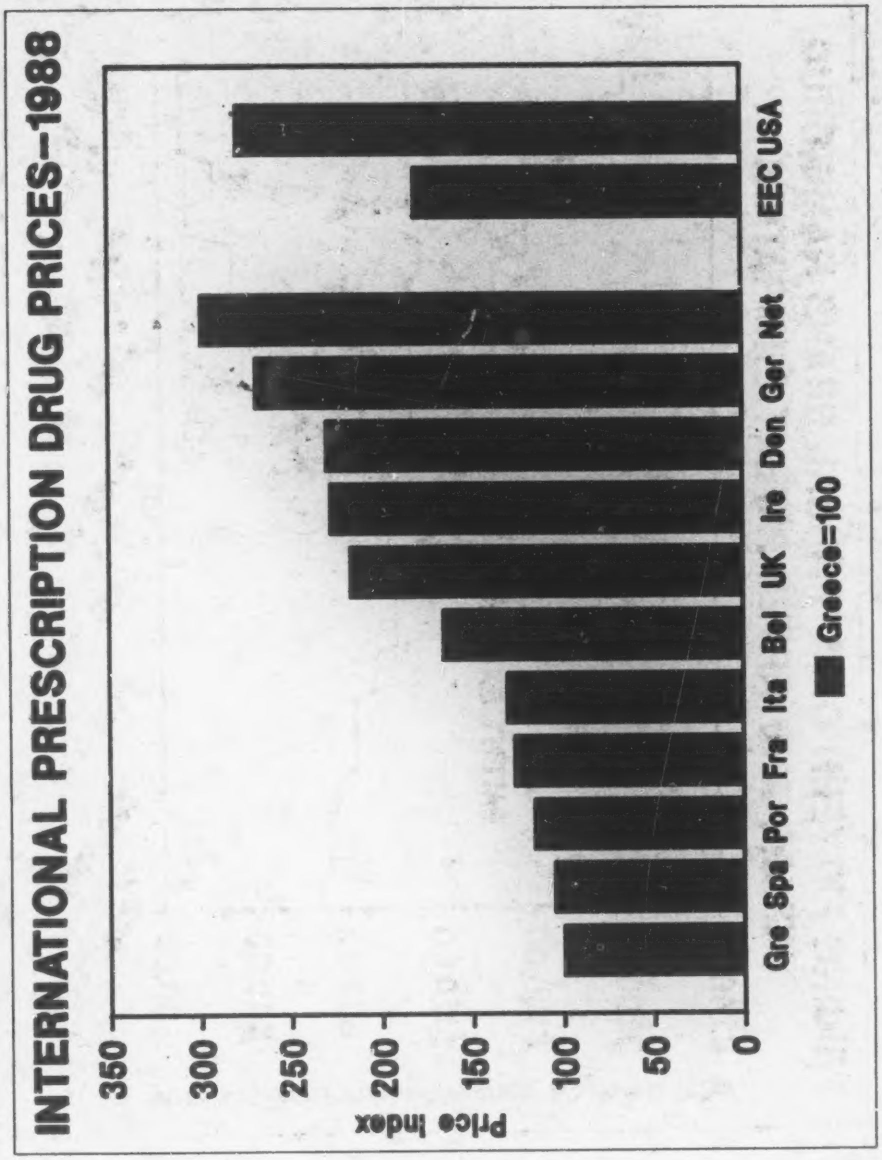
International Drug Price Comparison

Weighted Average Retail Price Per Brand Drug, 1987

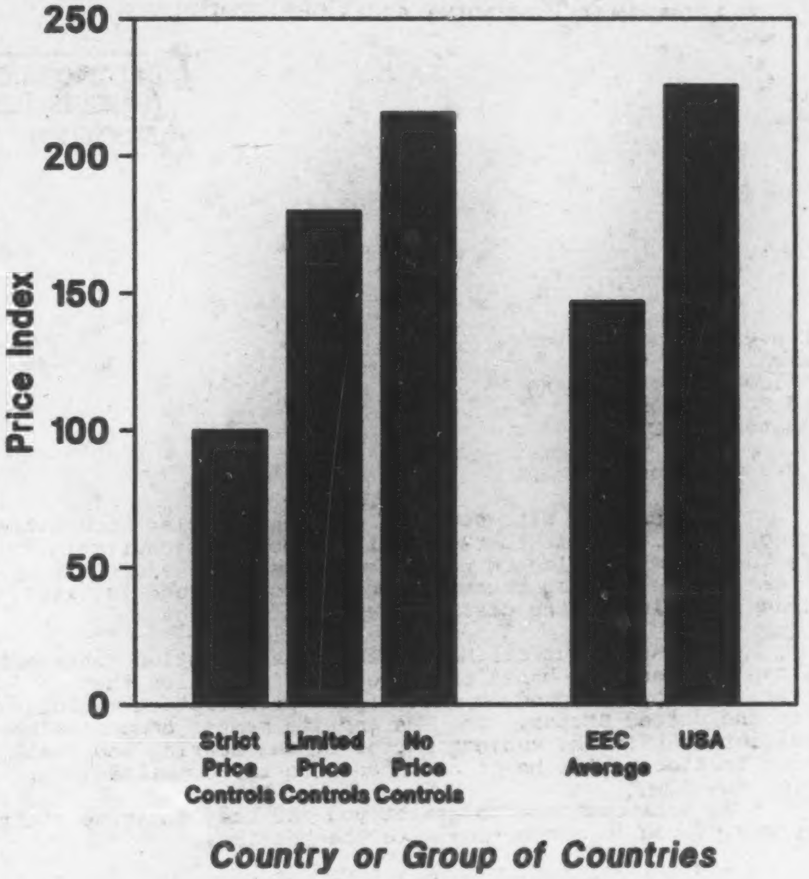
SOURCE: "Indicatori farmaceutici", annual survey of Farmindustria, the Italian pharmaceutical manufacturers association, published 1988.

PRICING PATTERN OF A TYPICAL BRAND NAME DRUG BEFORE AND AFTER PATENT EXPIRATION




INTERNATIONAL PRESCRIPTION DRUG PRICES--1988

IMPACT OF DRUG PRICE CONTROLS



NOTES: 1. Calculations based on weighted retail prices without VAT.
2. Cheapest Countries = 100.

APPENDIX 2

ADDITIONAL TESTIMONY AND CORRESPONDENCE

Pharmaceutical
Manufacturers
Association

Gerald J. Mossinghoff
PRESIDENT

May 25, 1989

The Honorable David Pryor
Chairman
Select Committee on Aging
United States Senate
Washington, D. C. 20510

Dear Mr. Chairman:

As discussed with staff of the Senate Select Committee on Aging, this letter is to request that the Pharmaceutical Manufacturers Association be permitted to testify before the Committee at the hearing presently scheduled for June 22, 1989, on issues relating to the cost of prescription drugs.

The Pharmaceutical Manufacturers Association represents more than 100 research-based pharmaceutical companies that discover, develop and produce most of the prescription medicines used in the United States. The PMA and its member companies have a vital interest in the subject matter of the hearing and feel that our testimony will be of assistance to the Committee.

We will continue to assist you and the Committee staff in any way we can in connection with the hearings.

Sincerely,

Gerald J. Mossinghoff

cc: The Honorable John Heinz

1100 Fifteenth Street NW, Washington, DC 20005 • Tel: 202-835-3420 • TWX: 7108229494-PMAWSH

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PORTIA PORTER MITTELMAN, STAFF DIRECTOR
CHRISTOPHER C. JENNINGS, DEPUTY STAFF DIRECTOR
[illegible], ACTING MINORITY STAFF DIRECTOR

United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

June 2, 1989

Mr. Dennis M. Styrsky (904 E)
Chief, Pharmaceutical Products Division
Department of Veterans' Affairs
Marketing Center
P.O. Box 76
Hines, IL 60141

Dear Mr. Styrsky:

On Thursday, June 22, 1989, the Senate Special Committee on Aging will convene a hearing on the subject of prescription drug manufacturer pricing policies and practices. I would like to take this opportunity to invite you to appear before the Committee to testify on this subject. I also request that you provide the Committee with materials, described below, which will assist us in our examination of this important issue.

This hearing will examine factors contributing to prescription drug cost increases in recent years, and explore opportunities in the current marketplace for third party payors, service providers and others to negotiate prescription drug purchase prices with manufacturers. Examples of negotiated prices of interest to the Committee include price discounts afforded by manufacturers to government agencies, such as the Department of Veterans' Affairs (DVA) and Department of Defense, and to health care providers and buying groups, including hospitals, Health Maintenance Organizations, and retail pharmacies.

Committee Members would appreciate hearing your views on a number of issues related to prescription drug pricing, based upon your experience in managing the DVA's prescription drug procurements for many years. In particular, your testimony should address the following questions:

1. Please provide the most recent price paid by DVA for each of the prescription drugs listed on the enclosed schedule (please note that this list is identical to the list provided to you by Committee staff on May 30). To facilitate our analysis of this data, please provide this information to Committee staff by close of business on June 9, 1989.

2. In general, what is magnitude of discounts realized by VA (expressed as a percentage of the Average Wholesale Price published in the U.S. at the time of DVA's purchase) as a result of its negotiations with manufacturers for procurement of (a) multiple source and (b) single source prescription drugs?

3. During the period 1981 - 1988, what has been the approximate annual rate of increase in prices paid by DVA for those prescription drugs purchased through negotiations with drug manufacturers?

4. Does DVA sometimes find it necessary to purchase prescription drugs at prices which are not negotiated with the drug manufacturer? If so, please indicate the reasons and/or circumstances under which DVA would purchase a prescription drug at a non-negotiated price, and the price paid (or basis for establishing the price paid) by DVA for prescription drugs under these circumstances.

5. What problems has the DVA encountered in attempting to negotiate favorable prices with manufacturers of multiple source and single source drugs? How has DVA attempted to resolve these problems?

6. In preparing for or conducting negotiations with prescription drug manufacturers, does DVA utilize information on prices paid by other governmental purchasers of prescription drug products (a) in the United States and (b) by foreign governments? Would such information be useful to DVA in its negotiations?

The Committee's hearing is scheduled to begin at 9:30 a.m. in room SD-562 of the Dirksen Senate Office Building. I would very much appreciate your providing the Committee with ten copies of your written testimony by close of business on June 19, and an additional 100 copies on the morning of June 21, 1989. Your testimony for submission into the record may be of whatever length you deem appropriate. The Committee would, however, appreciate your limiting oral remarks to no more than five minutes.

Thank you for your cooperation and assistance in this inquiry by the Committee. Should you have questions relating to this invitation and request for information, please contact David Schulke of the Special Committee on Aging staff at 202-224-5364.

Sincerely,

David Pryor

David Pryor
Chairman

Enclosure
DP:dgs

Multiple Source Drugs

Brand Name (Generic)	Strength	Dosage Form	Package Size
Tenormin (Atenolol)	50mg	tab	100
Dyazide (HCTZ & Triamterene)	50mg/25mg	cap	1000
Influenza Virus Vaccine type A, B.	----	inject.	5cc
Isordil (Isosorbide Dinitrate)	10mg	tab	100
Micro-K Extencaps (KCl)	10mg	SRcap	100
Lasix (Furosemide)	40mg	tab	1000
Inderal (Propranolol)	20mg	tab	100
Hydrodiuril (HCTZ)	50mg	tab	100
Motrin/Rufen (Ibuprofen)	800mg	tab	100
Deltasone (Prednisone)	5mg	tab	500
Aldomet (Methyldopa)	250mg	tab	100
Bactrim DS/Septra DS (Trimethoprim w/ sulfamethoxazole)	160mg/800mg	tab	100
Diabenese (Chlorpropamide)	250mg	tab	100
Theo-Dur (Theophylline)	300mg	SRtab	100

Keflex (Cephalexin)	500mg	cap	100
Antivert (Meclizine)	25mg	tab	100
Darvocet N (Propoxyphene Napsylate w/ Acetaminophen)	100mg/650mg	tab	500
Indocin (Indomethacin)	25mg	cap	100
Achromycin V (Tetracycline)	250mg	cap	100
Aldoril (HCTZ w/ methyldopa)	25mg/250mg	tab	100
Maxitrol (Dexamethasone, Neomycin, polymixin)	0.1%	opth. susp.	5cc
Valium (Diazepam)	5mg	tab	500
Zyloprim (Allopurinol)	300mg	tab	100
Ativan (Lorazepam)	1mg	tab	100
Tolinase (Tolazamide)	250mg	tab	100
E-Mycin (Erythromycin)	333mg	ECtab	100
Polycillin (Ampicillin)	500mg	cap	500
Amoxil (Amoxicillin)	500mg	cap	100
Hygroton (Chlorthalidone)	50mg	tab	100
Elavil (Amitiptyline)	25mg	tab	100

SINGLE SOURCE DRUGS

Brand	Strength	Dosage Form	Package Size
Lanoxin	0.25mg	tab	1000
Persantine	50mg	tab	100
Timoptic	0.5%	opth. sol.	10cc
Naprosyn	375mg	tab	100
Lopressor	50mg	tab	100
Synthroid	0.1mg	tab	100
Feldene	20mg	cap	100
Procardia	10mg	cap	300
Cardizem	60mg	tab	100
Transderm-Nitro	5mg	transdermal patch	30
Capoten	25mg	tab	100

[The following was received from the
Department of Veterans Affairs, in
response to Sen. Pryor's letter of
invitation to Mr. Styrsky.]

QUESTIONS AND ANSWERS

FOR

SPECIAL COMMITTEE ON AGING

PLEASE SEE ATTACHED PAGES

QUESTION NUMBER 1:

Please provide the most recent price paid by DVA for each of the prescription drugs listed on the enclosed schedule.

ANSWER TO QUESTION NUMBER 1:

SEE ATTACHED LISTINGS

[COMMITTEE STAFF NOTE: The "AMP Price" listed in these DVA price lists are not the published "AMP", but averages. The "FSS Price" is the price negotiated for the Federal Supply Schedule by DVA.]

NOMENCLATURE (GENERIC) AMP PRICE FSS PRICE PERCENTAGE +/- COMMENTS

NOMENCLATURE (GENERIC)		AMP PRICE	FSS PRICE	PERCENTAGE +/-	COMMENTS
ATENOLOL, 50 MG, 100		$56.17	$39.40	-27%	ICI PHARM.
FUROSEMIDE, 40 MG, 1000	AVG	$30.42	$7.39	-76%	BARR
	LOW	$8.34 (QUALITEST)			
IBUPROFEN, 800 MG, 100	AVG	$19.17	$5.00	-74%	UPJOHN
	LOW	$10.06 (HARTEC)			
CEPHALEXIN, 500 MG, 100	AVG	$81.13	$22.54	-72%	BARR
	LOW	$35.48 (GENETCO)			
PROPOXYPHENE NAPSYLATE W/APAP 100 MG/650 MG, 500	AVG	$88.00	$31.99	-64%	GOLDLINE
	LOW	$42.75 (INTERSTATE)			
INDOMETHACIN CAPS, 25 MG, 100	AVG	$11.48	$1.76	-85%	ZENITH
	LOW	$3.55 (QUALITEST)			
DIAZEPAM TABS, 5 MG, 500	AVG	$29.09	$3.85	-87%	RUGBY
	LOW	$6.54 (QUALITEST)			
ALLOP[illegible] TABS, 300 MG, 100	AVG	$18.95	$5.88	-69%	BARR
	LOW	$11.29 (QUALITEST)			
LORAZEPAM/[illegible], 1 MG, 100	AVG	$13.80	$2.70	-80%	RUGBY
	LOW	$3.75 (GENETCO)			
DIGOXIN TABS, .25 MG, 1000		$59.93	$6.98	-88%	FSS - GENERIC - RUGBY DEPOT - BRAND NAME - NO FSS
NAPROXEN TABS, 375 MG, 100		$71.41	N/A		SYNTEX - NO FSS
NIFEDIPINE CAPS, 10 MG, 300	AVG	$106.01	$76.14	-28%	PFIZER
	LOW	$104.46 (PFIZER)			
DILTIAZEM TABS; 60 MG, 100		$44.38	$33.00	-26%	MARION
NITROGLYCERIN TRANSDERMAL SYS 5 MG 30		$36.22	$3.90 $4.00	-89%	SEARLE CIBA
[illegible]TOPRIL TABS, 25 MG, 100		$40.00	$31.89	-20%	SQUIBB
[illegible] CMP, 50 MG/25 MG, 1000 ([illegible]HCTZ & TRIAMT[illegible])	AVG	$227.23	$50.00	-78%	SEE SK&F CO. (ITEM 3590-30)
	LOW	$[illegible]35.94			
ISORDIL TABS, 10 MG, 100 (ISOSORBIDE DINITRATE)		$3.24	$0.75	-77%	SEE FSC GROUP 65 PART I SECTION A DEPOT PRICE $1.65/500 ($0.33/100)
MICRO-K EXTENCAPS SR, 10 MG, 100 (KCL)		$10.04	$7.66	-24%	SEE A.H.ROBINS (ITEM 5730-60 NOT IN TOP TEN)

NOMENCLATURE (GENERIC)		AWP PRICE	FSS PRICE	PERCENTAGE +/-	COMMENTS
INDERAL TAB, 20 MG, 100 (PROPRANOLOL)		$11.58	$0.76	-93%	SEE FSC GROUP 65 PART I SECTION A DEPOT PRICE $3.60/1000 ($0.36/100)
HYDRODIURIL TAB, 50 MG, 100 (HCTZ)	AVG LOW	$2.76 $1.13	$0.90 N/A MSD	-67%	SEE RUGBY LABS. (ITEM NOT IN TOP TEN) DEPOT PRICE $2.63/1000 ($0.263/100)
DELTASONE TAB, 5 MG, 500 (PREDNISONE)		$7.99 ($15.97/1000)	$3.65 ($7.30/1000)	-54%	SEE FSC GROUP 65 PART I SECTION A
ALDOMET TAB, 250 MG, 100 (METHYLDOPA)	AVG LOW	$14.63 $7.28	$5.10 $19.69 MSD	-65%	SEE RUGBY LABS. (ITEM NOT IN TOP TEN) (ITEM NOT IN MSD TOP TEN)
BACTRIM/SEPTRA TAB, 160/800 MG, 100 (TRIMETH/SULFAMETHOXAZOLE)	AVG LOW	$21.64 $7.84	$5.05 N/A B-W $15.12 ROCHE	-77%	SEE LEMMON CO. (ITEM 0189-01) DEPOT PRICE $20.55/500 ($4.11/100) SEE ROCHE LABS (ITEM 72414)
DIABINESE TAB, 250 MG, 100 (CHLORPROPAMIDE)	AVG LOW	$7.36 $2.48	$1.80 N/A PFIZER	-76%	SEE RUGBY LABS. (ITEM NOT IN TOP TEN) DEPOT PRICE $2.35/250 ($0.94/100)
THEO-DUR SR TAB, 300 MG, 100 (THEOPHYLLINE)	AVG LOW	$18.88 $17.02	$3.25 $4.91 SCHERING	-83%	SEE RIKER LABS (ITEM 0343-10) (ITEM ADDED BY MODIFICATION - NO DSMD)
ANTIVERT TAB, 25 MG, 100 (MECLIZINE)	AVG LOW	$3.86 $1.52	$1.40 N/A PFIZER	-64%	SEE GOLDLINE LABS (ITEM 15210 NOT IN TOP TEN)
ACHROMYCIN V CAP, 250 MG, 100 (TETRACYCLINE)		$4.34	$1.87	-57%	SEE FSC GROUP 65 PART I SECTION A
ALDORIL TAB, 25MG/250 MG, 100 (HCTZ W/METHYLDOPA)	AVG LOW	$24.19 $15.54	$11.00 $27.63 MSD	-55%	SEE RUGBY LABS. (ITEM NOT IN TOP TEN) (ITEM NOT IN MSD TOP TEN)
TOLINASE TAB, 250 MG, 100 (TOLAZAMIDE)	AVG LOW	$20.23 $6.75	$6.05 $26.12 UPJOHN	-70%	SEE ZENITH LABS (ITEM 2979-60 NOT IN TOP TEN) DEPOT PRICE $44.00/1000 ($4.40/100) (ITEM NOT IN UPJOHN TOP TEN)
POLYCILLIN CAP, 500 MG, 500 (AMPICILLIN)		$71.98	$30.75	-57%	SEE FSC GROUP 65 PART I SECTION A DEPOT PRICE $5.64/100 ($28.20/500)
AMOXIL CAP, 500 MG, 100 (AMOXICILLIN)		$44.06	$8.50	-81%	SEE FSC GROUP 65 PART I SECTION A DEPOT PRICE $32.00/500 ($6.40/100)
HYGROTON TAB, 50 MG, 100 (CHLORTHALIDONE)		$7.76	$1.75	-77%	SEE FSC GROUP 65 PART I SECTION A DEPOT PRICE $11.15/1000 ($1.115/100)
ELAVIL TAB, 25 MG, 100 (AMITRIPTYLINE)		$3.75	$0.80	-79%	SEE FSC GROUP 65 PART I SECTION A DEPOT PRICE $4.30/1000 ($0.43/100)
PERSANTINE TABS, 50 MG, 100 (DIPYRIDAMOLE)		$6.97	$1.22	-82%	SEE FSC GROUP 65 PART I SECTION A
TIMOPTIC OPTH SOL, 0.5%, 10 ML		$24.65	$19.12	-22%	SEE MERCK SHARP & DOHME (ITEM 336710 NOT IN TOP TEN)
LOPRESSOR TABS, 50 MG, 100		$36.40	$23.65	-35%	SEE GEIGY (ITEM 3601 NOT IN TOP TEN) DEPOT PRICE $126.17/1000 ($12.617/100)
FELDENE CAPS, 20 MG, 100		$154.76	$112.79	-27%	SEE PFIZER (ITEM 1292) DEPOT PRICE $420.06/500 ($84.01/100)
FAMOTIDINE TABS, 40 MG, 30		$63.41	$50.73	-20%	MERCK SHARP & DOHME
CIMETIDINE TABS, 300 MG, 100		$49.95	N/A		SK&F LAB CO.
RANITIDINE TABS, 150 MG, 60		$73.63	$34.16	-54%	SEE GLAXO - ITEM 0344-42
RANITIDINE TABS, 300 MG, 30		$63.40	$41.46	-35%	SEE GLAXO - ITEM NOT IN TOP TEN

[COMMITTEE STAFF NOTE: The drug price histories appearing on this and following pages are based on DVA's Depot system, not the Federal Supply Schedule prices. Depot prices are lower.]

NOMENCLATURE		AMP	81	82	83	84	85	86	87	88	89	+/-
NOMENCLATURE		AMP	81	82	83	84	85	86	87	88	89	+/-
ATENOLOL, 50 MG, 100		$54.17	NDS	NDS	NDS	NDS	$23.30 *	$26.35 *	$26.75 *	$31.33 *	$31.33 *	34%
+/- (CURRENT VS AMP)(YR TO YR)		-42%						14%	1%	17%	0%	
FUROSEMIDE, 40 MG, 1000	AVG	$30.42	NDS	$23.10	$19.75	$9.00	$7.69	$6.12	$5.99	$5.87	$5.47	-76%
	LOW	$8.34										
+/- (CURRENT VS AMP)(YR TO YR)		-82%			-15%	-54%	-15%	-20%	-2%	-2%	-7%	
IBUPROFEN, 800 MG, 100	AVG	$19.17	NDS	NDS	NDS	NDS	$6.80 *	$6.80 *	$3.49	$2.46	$2.31	-66%
	LOW	$10.04										
+/- (CURRENT VS AMP)(YR TO YR)		-88%						0%	-49%	-30%	-6%	
CEPHALEXIN, 500 MG, 100	AVG	$81.13	$46.51 *	$51.21 *	$57.36 *	$66.87 *	$66.87 *	$66.87 *	$66.87 *	$18.00	$13.97	-70%
	LOW	$35.48										
+/- (CURRENT VS AMP)(YR TO YR)		-83%		10%	12%	17%	0%	0%	0%	-73%	-22%	
PROPOXYPHENE NAPSYLATE W/APAP 100 MG/650 MG, 500	AVG	$80.00	$20.36 *	$23.63 *	$29.54 *	$38.34 *	$38.34 *	$17.99	$17.50	$15.80	$13.25	-35%
	LOW	$42.75										
+/- (CURRENT VS AMP)(YR TO YR)		-83%		16%	25%	30%	0%	-53%	-2%	-10%	-16%	
INDOMETHACIN CAPS, 25 MG, 100	AVG	$11.40	NDS	NDS	NDS	$5.00	$1.60	$1.41	$1.27	$1.16	$1.16	-77%
	LOW	$3.55										
+/- (CURRENT VS AMP)(YR TO YR)		-90%					-68%	-12%	-10%	-9%	0%	
DIAZEPAM TABS, 5 MG, 500	AVG	$29.09	$22.76 *	$25.63 *	$28.47 *	$40.05 *	$51.26 *	$5.99	$3.35	$2.79	$2.79	-88%
	LOW	$6.54										
+/- (CURRENT VS AMP)(YR TO YR)		-90%		13%	11%	41%	28%	-88%	-41%	-21%	0%	
ALLOPURINOL TABS, 300 MG, 100	AVG	$18.95	$11.33	$8.45	$7.75	$7.90	$6.99	$6.34	$5.80	$4.06	$4.06	-64%
	LOW	11.29										
+/- (CURRENT VS AMP)(YR TO YR)		-79%		-29%	-8%	2%	-12%	-9%	-9%	-30%	0%	

NOMENCLATURE		AMP	81	82	83	84	85	86	87	88	89	+/-
LORAZEPAM TABS, 1 MG, 100	AVG	$13.80	NDS	NDS	NDS	$14.23 *	$20.16 *	$20.16 *	$1.19	$0.99	$0.99	-93%
	LOW	$3.75										
+/- (CURRENT VS AMP)(YR TO YR)		-93%					42%	0%	-94%	-17%	0%	
DIGOXIN TABS, .25 MG, 1000		$59.93	$6.15 *	$8.76 *	$10.89 *	$14.88 *	$19.07 *	$22.88 *	$38.25 *	$41.89 *	$46.50 *	656%
+/- (CURRENT VS AMP)(YR TO YR)		-22%		42%	24%	37%	28%	20%	67%	10%	11%	
NAPROXEN TABS, 375 MG, 100		$71.41	NDS	$30.78 *	$30.78 *	$31.45 *	$32.71 *	$33.53 *	$33.53 *	$34.54 *	$35.58 *	16%
+/- (CURRENT VS AMP)(YR TO YR)		-50%			0%	2%	4%	3%	0%	3%	3%	
NIFEDIPINE CAPS, 10 MG, 300	AVG	$106.01	NDS	NDS	NDS	NDS	NDS	$54.60	$59.92	$64.72	$64.72	19%
	LOW	$104.46										
+/- (CURRENT VS AMP)(YR TO YR)		-39%							10%	8%	0%	
DILITIAZEM TABS, 60 MG, 100		$44.38	NDS	NDS	$22.10 *	$22.55 *	$24.70 *	$26.90 *	$27.15 *	$28.05 *	$28.38 *	28%
+/- (CURRENT VS AMP)(YR TO YR)		-36%				2%	10%	9%	1%	3%	1%	
NITROGLYCERIN TRANSDERMAL SYS 5 MG 30		$36.22	NDS	NDS	NDS	NDS	NDS	NDS	NDS	NDS	$3.60 *	
+/- (CURRENT VS AMP)		-90%										
CAPTOPRIL TABS, 25 MG, 100		$40.00	NDS	NDS	NDS	NDS	NDS	NDS	NDS	NDS	$28.38 *	
+/- (CURRENT VS AMP)		-29%										
FAMOTIDINE TABS, 40 MG, 30		$63.41	NDS	NDS	NDS	NDS	NDS	NDS	NDS	NDS	$45.66 *	
+/- (CURRENT VS AMP)		-28%										
CIMETIDINE TABS, 300 MG, 100		$49.95	NDS	20.43 *	21.99 *	21.99 *	24.63 *	27.09 *	27.09 *	27.09 *	27.09 *	10%
+/- (CURRENT VS AMP)(YR TO YR)		-46%			8%	0%	12%	10%	0%	0%	0%	

*DENOTES SINGLE SOURCE

NDS DENOTES NOT DEPOT STOCKED

LOWEST AMP IS SHOWN FOR INFORMATIONAL PURPOSES ONLY - PERCENTAGES ARE BASED ON AVG AMP

Multiple Award

Federal Supply Schedule

CUMULATIVE EDITION/APRIL 25, 1989 **365C 6501**

DRUGS AND PHARMACEUTICAL PRODUCTS

FSC GROUP 65 PART I, SECTION A, FSC CLASS 6501
For the period July 1, 1988 – June 30, 1989

GEOGRAPHIC COVERAGE—The 50 States; Washington, DC; and the Commonwealth of Puerto Rico.

This document replaces the Cumulative Edition issued January 30, 1989.

Veterans Administration
Office of Procurement and Supply

AMINOPHYLLINE USP TABLETS (*SB Set-Aside)

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
	100 mg			
14	100's*			
	Whitworth/TN Paulsen (Min order 12)	0167-0386-01	EA	0.99
	Whitworth/TN Paulsen	0157-0386-01	EA	1.04
	Consolidated Midland	0223-0100-01	EA	1.30
	AVERAGE COMMERCIAL PRICE			1.97
15	1000's*			
	Purepac	0536-3053-10	BT	4.50
	U S Trading	0143-1020-10	EA	4.96
	IDE	0814-0625-30	EA	5.77
	Moore	00839-5053-16	EA	5.85
	Jameson Pharm	0115-2150-03	BT	5.80
	Whitworth/TN Paulsen (Min order 12)	0157-0386-10	EA	6.07
	Whitworth/TN Paulsen	0157-0386-10	EA	6.25
	Goldline (6 or more)	0182-0100-10	EA	6.74
	Goldline	0182-0100-10	EA	6.96
	Consolidated Midland	0223-0100-02	EA	6.95
	West-Ward	0143-1020-10	EA	7.13
	AVERAGE COMMERCIAL PRICE			11.80
	200 mg			
16	100's*			
	U S Trading	0143-1025-01	EA	1.20
	Whitworth/TN Paulsen (Min order 12)	0157-0399-01	EA	1.27
	Whitworth/TN Paulsen	0157-0399-01	EA	1.30
	Consolidated Midland	0223-0101-01	EA	1.90
	West-Ward	0143-1025-01	EA	2.33
	AVERAGE COMMERCIAL PRICE			2.84
17	Unit Dose/100's*			
	Jameson Pharm	0143-1025-25	EA	4.62
	West-Ward	0143-1025-25	EA	2.95
	US Trading	0143-1025-05	EA	2.76
	AVERAGE COMMERCIAL PRICE			4.88
18	1000's*			
	Purepac	0536-1011-10	BT	7.50
	Jameson Pharm	0115-2150-05	BT	8.23
	Whitworth/TN Paulsen (Min order 12)	0157-0399-10	EA	8.40
	Whitworth/TN Paulsen	0157-0399-10	EA	8.72
	Goldline (6 or more)	0182-0110-10	EA	9.30
	Goldline	0182-0110-10	EA	9.50
	West-Ward	0143-1025-10	EA	9.60
	IDE	0814-0627-30	EA	9.73
	Consolidated Midland	0223-0101-02	EA	10.95
	AVERAGE COMMERCIAL PRICE			17.80

AMITRIPTYLINE HCL, USP. TABLETS (SB Set-Aside)

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
	25 mg			
19	100's			
	Purepac	0228-0130-00	BT	.80
	Moore	00839-6105-06	EA	.83
	MD Pharm Inc*	43567-638-07	EA	0.86
	Biocraft	0332-2122-00	EA	.88
	Mylan	0378-2625-01	BT	.95
	US Trading	49884-134-01	EA	.99
	MLC	0839-2128-00	EA	1.05
	UDL	51079-107-40	EA	1.16
	Halsey	0489-01	EA	1.25
	Whitworth/TN Paulsen (Min order 12)	0157-0387-01	EA	1.28
	Whitworth/TN Paulsen	0157-0387-01	EA	1.28
	IDE	0814-0636-30	EA	1.42
	Jameson Pharm	00111-387-01	BT	1.43
	Goldline (12 or more)	0182-1018-01	EA	1.66
	Rugby (Min order 48)	0536-2123-06	EA	1.80
	Goldline	0182-1018-01	EA	1.90
	Consolidated Midland	0223-0106-01	EA	1.80
	AVERAGE COMMERCIAL PRICE			3.75
20	1000's			
	NO AWARD			
21	Unit Dose/100's			
	Goldline Labs	0182-1018-89	EA	2.30
	UDL	51079-107-20	EA	2.25
	Vangard	0615-0550-13	EA	2.38
	US Trading	53622-134-11	EA	2.75
	Pro-Care 10 x 10	53989-050-75	EA	2.90
	Rugby (Min order 24)	51079-107-20	EA	4.86
	Jameson Pharm	0378-402-01	EA	4.22
	Consolidated Midland	0223-010-00	EA	8.75
	AVERAGE COMMERCIAL PRICE			11.87
	50 mg			
22	100's			
	Biocraft	0332-2124-00	EA	1.10
	MD Pharm Inc*	43567-640-07	EA	1.17
	Mylan	0378-2650-01	BT	1.30
	Purepac	0228-2130-06	BT	1.32
	MLC	0839-2124-00	EA	1.35
	Moore	00839-6130-06	EA	1.43
	US Trading	49884-135-01	EA	1.44
	Halsey	0489-01	EA	1.56
	UDL	51079-138-40	EA	1.58
	Whitworth/TN Paulsen (Min order 12)	0157-0388-01	EA	1.73
	Whitworth/TN Paulsen	0157-0388-01	EA	1.78
	IDE	0814-0638-30	EA	1.98
	Jameson Pharm	00111-388-01	BT	1.95

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
	Goldline	0182-1020-01	EA	1.30
	(12 or more)			
	Goldline	0182-1020-01	EA	2.10
	Rowey	0332-2124-09	EA	2.24
	(Min order 24)			
	Consolidated Midland	0223-0107-01	EA	2.50
	AVERAGE COMMERCIAL PRICE			10.56
23	1000's			
	NO AWARD			
24	Unit Dose/100's			
	Goldline Labs	0182-1020-89	EA	2.80
	UDL	51079-133-20	EA	2.86
	Vangard	0615-0630-13	EA	2.90
	US Trading	49884-136-11	EA	2.99
	Pro-Care	53269-021-45	EA	3.20
	10 x 10			
	Rowey	51079-133-20	EA	4.50
	(Min order 12)			
	Jameson Pharm	0679-0480-01	EA	5.50
	Consolidated Midland	0223-0107-00	EA	6.50
	AVERAGE COMMERCIAL PRICE			15.80
	75 mg			
25	100's			
	Biocraft	0332-2129-70	EA	1.80
	Mylan	0378-2675-01	BT	1.85
	MD Pharm Inc*	43567-541-07	EA	1.86
	MLC	0332-2129-09	EA	1.97
	Rugby	0536-6194-06	BT	2.00
	US Trading	49884-036-01	EA	2.04
	Moore	00839-6194-06	EA	2.15
	Whitworth/TN Paulsen	0157-0369-01	EA	2.67
	(Min order 12)			
	Whitworth/TN Paulsen	0157-0369-01	EA	2.75
	Halsey	0491-01	EA	2.75
	Jameson Pharm	50111-369-02	BT	2.90
	Rowey	0332-2129-01	EA	3.00
	(Min order 24)			
	IDE	0814-0842-14	EA	3.15
	Goldline	0182-1021-01	EA	2.25
	(12 or more)			
	Goldline	0182-1021-01	EA	3.55
	Consolidated Midland	0223-0108-01	EA	3.75
	AVERAGE COMMERCIAL PRICE			15.46
26	Unit Dose/100's			
	Goldline Labs	0182-1021-89	EA	4.60
	US Trading	53633-136-11	EA	3.44
	UDL	51079-147-20	EA	3.45
	Vangard	0615-0631-13	EA	4.10
	Pro-Care	53269-022-75	EA	4.86
	10 x 10			
	Jameson Pharm	0143-3049-25	EA	6.65
	US Trading	0143-3049-25	EA	6.65
	Rowey	51079-147-20	EA	7.00
	(Min order 24)			
	Consolidated Midland	0223-0108-01	EA	8.50
	AVERAGE COMMERCIAL PRICE			27.63
	100 mg			
27	100's			
	Biocraft	0332-2128-09	EA	1.95
	~~Mylan~~	~~0378-0686-01~~	BT	~~2.36~~
	MLC	0332-2128-09	EA	2.43
	Rugby	0536-6223-06	BT	2.55
	Moore	00839-6223-06	EA	2.57
	US Trading	49884-137-01	EA	2.70
	MD Pharm Inc*	43567-542-07	EA	2.95
	Rowey	0332-2128-09	EA	3.35
	(Min order 24)			
	Whitworth/TN Paulsen	0157-0370-01	EA	3.53
	(Min order 12)			
	Whitworth/TN Paulsen	0157-0370-01	EA	3.64
	Halsey	0492-01	EA	3.75
	Jameson Pharm	50111-370-01	BT	3.96
	IDE	0814-0843-14	EA	4.12
	Consolidated Midland	0223-0109-01	EA	5.75
	AVERAGE COMMERCIAL PRICE			19.56
28	Unit Dose/100's			
	Goldline Labs	0182-1082-89	EA	4.06
	US Trading	53633-137-11	EA	4.50
	UDL	51079-563-20	EA	4.71
	Vangard	0615-0632-13	EA	4.80
	Pro-care	53269-023-75	EA	6.26
	10 x 10			
	Rowey	51079-563-20	EA	8.96
	(Min order 12)			
	Consolidated Midland	0223-0109-06	EA	12.50
	AVERAGE COMMERCIAL PRICE			40.63
	150 mg			
29	100's			
	US Trading	49884-138-01	EA	3.66
	MD Pharm Inc*	4357-543-07	EA	3.95
	Rugby	0536-6401-06	BT	4.60
	Moore	00839-6401-06	EA	5.07
	Whitworth/TN Paulsen	0157-0371-01	EA	5.20
	(Min order 12)			
	Goldline	0182-1140-01	EA	4.25
	(12 or more)			
	Whitworth/TN Paulsen	0157-0371-01	EA	5.35
	Goldline	0182-1140-01	EA	4.25
	Jameson Pharm	50111-371-01	BT	5.85
	IDE	0814-0844-14	BT	6.00
	Mylan	0378-0204-01	BT	6.35
	Consolidated Midland	0223-0110-01	EA	8.50
	AVERAGE COMMERCIAL PRICE			28.78

AMOXICILLIN CAPSULES

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
	250 mg			
30	100's			
	Biocraft	0332-3107-09	EA	4.25
	Best Generics	0839-3107-09	EA	5.95
	(max order 24)			
	Squibb	0003-0830-09	EA	6.07
	US Trading	0378-0204-01	EA	6.25
	Kaye Pharm	0332-3107-09	BT	6.35

Index No.	Description/ Quantity/ Contractor	National Drug Code	Unit of Issue	Price ($) Each
	Mylan	0378-0604-01	BT	6.25
	Lypho-Med	5452-3724-40	EA	6.40
	Purepac	0052-0007-00	BT	6.95
	Warner-Chilcott	0047-0730-04	EA	6.67
	MLC	0332-3107-05	EA	6.90
	Schein	0364-2040-01	EA	7.11
	Rugby	0536-0070-01	EA	7.16
	Wyeth Labs	0008-0559-01	EA	7.55
	Jameson Pharm	0332-3107-05	BT	7.64
	Lederle	0005-3144-05	EA	7.73
	Geneva	0781-222501	EA	8.05
	Beecham	0000-30	BT	8.28
	Goldline	0182-1070-01	EA	7.10
	(12 or more)			
	Goldline	0182-1070-01	EA	8.25
	Rexall	0332-3107-00	EA	9.63
	(Min order 24)			
	AVERAGE COMMERCIAL PRICE			16.73
31	500's			
	Biocraft	0332-3107-13	EA	21.00
	Squibb	0003-0236-00	EA	26.50
	Best Generics	0332-3107-13	EA	28.25
	(Max order 12)			
	Wyeth Labs	0008-0559-02	EA	28.50
	Kaye Pharm	0332-3107-13	BT	29.20
	US Trading	0378-0604-05	EA	29.20
	Warner-Chilcott	0047-0730-30	EA	29.23
	Mylan	0378-0604-05	BT	29.45
	Lypho-Med	5452-3724-70	EA	30.65
	Purepac	0228-0037-12	BT	30.90
	MLC	0332-3107-13	EA	32.73
	Schein	0364-2040-05	EA	33.12
	Rugby	0536-0070-05	EA	35.00
	Jameson Pharm	0332-3107-13	BT	35.94
	Lederle	0005-3144-31	EA	36.25
	Geneva	0781-222205	EA	31.00
	Beecham	0000-32	BT	38.15
	Goldline	0182-1070-05	EA	35.00
	(6 or more)			
	Goldline	0182-1070-05	EA	44.95
	Rexall	0332-3107-13	EA	51.00
	(Min order 12)			
	AVERAGE COMMERCIAL PRICE			80.47
32	Unit Dose/100			
	Biocraft	0332-3107-65	EA	6.35
	UDL	51079-020-20	EA	8.10
	Squibb	0003-0229-51	EA	8.45
	Warner-Chilcott	0047-0730-40	EA	11.02
	Beecham	0000-31	BX	11.77
	AVERAGE COMMERCIAL PRICE			23.07
	500 mg			
33	100's			
	Biocraft	0332-3109-00	EA	8.50
	Lypho-Med	54623-71640	BT	10.50
	Warner-Chilcott	0047-0731-24	BT	12.56
	Beecham	0007-30	BT	15.97
	AVERAGE COMMERCIAL PRICE			44.56
34	500's			
	Biocraft	0332-3109-13	EA	42.00
	Lypho-Med	5452-3716-70	BT	51.61
	Squibb	0003-0231-00	EA	53.50
	Best Generics	0332-3109-13	EA	54.70
	(Max order 10)			
	Wyeth Labs	0008-0560-05	EA	57.00
	US Trading	0378-0608-05	EA	58.25
	Mylan	0378-0608-05	BT	58.35
	Kaye Pharm	0332-3107-13	BT	59.95
	Purepac	0228-0029-12	BT	59.95
	Schein	0364-2041-05	EA	63.00
	MLC	0332-3109-13	EA	64.03
	Jameson Pharm	0332-3109-13	BT	71.67
	Lederle	0005-3145-31	EA	72.50
	Beecham	0007-32	BT	75.41
	Goldline	0182-1071-05	EA	72.90
	(6 or more)			
	Goldline	0182-1071-05	EA	85.95
	Rexall	0332-3109-13	EA	80.50
	(Min order 12)			
	AVERAGE COMMERCIAL PRICE			163.92
35	Unit Dose/100			
	Biocraft	0332-3109-05	EA	10.50
	Lypho-Med	54623-71601	BX	11.66
	UDL	51079-001-20	EA	12.20
	Squibb	0003-0231-51	EA	12.50
	Warner-Chilcott	0047-0731-40	PKG	15.06
	Beecham	0007-31	BX	22.56
	AVERAGE COMMERCIAL PRICE			23.67

AMPICILLIN USP CAPSULES

Index No.	Description/ Quantity/ Contractor	National Drug Code	Unit of Issue	Price ($) Each
	250 mg			
36	100's			
	NO AWARD			
37	500's (Trade Agreement Act Applies)			
	NO AWARD			
38	1000's			
	Biocraft	0332-3111-15	EA	31.40
	Schein	0364-2001-02	EA	37.50
	Rugby	0536-0010-10	EA	38.25
	MLC	0332-3111-15	EA	38.40
	US Trading	0332-3111-15	EA	38.75
	Kaye Pharm	0332-3113-09	BT	39.95
	Goldline	0182-0100-10	EA	40.90
	(6 or more)			
	Jameson Pharm	0332-3111-15	BT	45.30
	Goldline	0182-0100-10	EA	40.50
	AVERAGE COMMERCIAL PRICE			82.75
39	Unit Dose/100's			
	NO AWARD			
	500 mg			

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
40	500's			
	Biocraft	0332-3113-13	EA	30.70
	Wyeth Labs	0008-0309-05	EA	33.25
	Squibb	0003-0874-61	EA	33.90
	Warner-Chilcott	0047-0464-30	BT	34.57
	Mylan	0378-0116-05	BT	36.80
	MLC	0332-3113-13	EA	39.60
	US Trading	0378-0116-05	EA	39.65
	Beecham	0029-32	BT	40.00
	Schein	0364-2002-05	EA	40.46
	Ponte	0839-6130-12	BT	40.76
	Best Generics (Max order 12)	0378-0116-05	EA	41.20
	Lederle	0005-3667-31	EA	42.33
	Kaye Pharm	0332-3113-13	BT	42.96
	Goldline (6 or more)	0182-0641-05	EA	40.93
	Geneva	0781-200005	EA	45.20
	Goldline	0182-0641-05	EA	45.50
	Jameson Pharm	0332-3113-13	BT	46.62
	AVERAGE COMMERCIAL PRICE			71.86

ANTIHEMOPHILIC FACTOR (HUMAN), USP

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
41	10 ml			
	AVERAGE COMMERCIAL PRICE			0.36
42	20 ml			
	AVERAGE COMMERCIAL PRICE			0.36
43	Unit Vial/500			
	AVERAGE COMMERCIAL PRICE			0.20

ASPIRIN, BUTALBITAL, CAFFEINE, 100'S

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
44	100's			
	Schein	0364-0677-01	EA	1.60
	Geneva	0781-142001	EA	1.73
	Rugby	0536-3637-01	EA	1.75
	Pure Pac	0228-2002-10	BT	1.80
	Halsey	0569-02	EA	1.80
	Jameson Pharm	0879-0000-01	EA	1.85
	US Trading	0143-1785-01	EA	1.90
	West-Ward	0143-1785-01	EA	2.10
	Goldline (12 or more)	0182-1631-01	EA	1.70
	Goldline	0182-1631-01	EA	2.00
	AVERAGE COMMERCIAL PRICE			3.65

ATROPINE INJECTION

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
45	1 ml			
	Elkins-Sinn (25 VL)	0641-0000-25	EA	.172
	Elkins-Sinn (100-Amp)	0641-1300-25	EA	.1770
	Elkins-Sinn (25-Amp)	0641-1300-35	EA	.178
	AVERAGE COMMERCIAL PRICE		AMP	0.20
	Lypho-Med	0469-034-025	VL	.23
	US Trading	0467-1234-25	EA	.25
	AVERAGE COMMERCIAL PRICE		VL	0.26
46	5 ml			
	AVERAGE COMMERCIAL PRICE		AMP	0.46
	Astra (5x10/Case*) *Shipments made in case qty	0186-0640-01	EA	3.60
	AVERAGE COMMERCIAL PRICE		DS SYR	44.67
47	30 ml			
	Elkins-Sinn	0641-0210-43	EA	.36
	Lypho-Med	0469-023426	VL	.40
	US Trading	0467-0024-35	EA	.70
	Jameson Pharm (25's)	0467-0024-25	EA	.71
	AVERAGE COMMERCIAL PRICE		VL	1.86

BETAMETHASONE VALERATE, TUBE

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
48	15 gm			
	US Trading (cream)	49502-080-35	EA	1.20
	US Trading (ointment)	49502-019-35	EA	1.20
	Best Generics (Max order 12)	54274-896-11	EA	1.25
	Ponte	0839-6371-47	TU	1.33
	Schein	0364-7289-72	EA	1.37
	UDL (cream)	51079-384-61	EA	1.45
	Jameson Pharm	49502-080-35	EA	1.64
	Geneva	0781-706527	EA	1.75
	Raway (Min order 288)(Cream)	24208-410-60	EA	2.35
	Raway (Min order 288)(Oint.)	24208-440-60	EA	2.38
	Rugby	0536-4310-30	EA	2.03
	AVERAGE COMMERCIAL PRICE			3.89

BETHANECHOL CHLORIDE TABLETS

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
	10 mg			
49	250's			
	Consolidated Midland	0223-0431-05	EA	7.90
	AVERAGE COMMERCIAL PRICE			7.91
50	1000's			
	Jameson Pharm	0011-384-05	BT	6.83
	Whitworth/TH Paulsen (Min order 12)	0157-0716-10	EA	7.02
	Whitworth/TH Paulsen	0157-0716-10	EA	7.24
	Vangard	0615-2557-10	EA	7.26
	US Trading	50111-384-10	EA	9.00
	Bolar	0725-0074-10	EA	9.75
	Best Generics (Max order 12)	0725-0074-10	EA	10.20
	Ponte	0839-0000-10	BT	10.40

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
	Whitworth/TN Paulsen (Min order 12)	0157-0723-05	EA	8.98
	Whitworth/TN Paulsen	0157-0723-05	EA	9.22
	US Trading	48684-078-05	EA	9.75
	Jameson Pharm	48094-078-05	EA	11.08
	IDE	0814-1700-30	EA	11.62
	Geneva	0781-162305	EA	9.95
	Consolidated Midland	0223-0667-05	EA	14.00
	AVERAGE COMMERCIAL PRICE			28.61
88	1000's			
	MLC	0832-0970-10	EA	11.50
	Vangard	0615-2641-10	EA	13.62
	Bolar	0725-0160-10	EA	14.00
	Zenith (con eff 10/17/88)	0172-2800-80	BT	14.45
	Ponta	0630-7012-16	BT	14.86
	Mylan	0378-0210-10	BT	15.50
	Goldline (6 or more)	0182-1052-10	EA	15.24
	Halsey	0603-10	EA	16.45
	Jameson Pharm	50111-373-03	BT	16.84
	Goldline	0182-1052-10	EA	16.86
	Whitworth/TN Paulsen (Min order 12)	0157-0723-10	EA	17.33
	Moore	00839-7012-16	EA	17.73
	Whitworth/TN Paulsen	0157-0723-10	EA	17.84
	Geneva	0781-162310	EA	18.90
	IDE	0814-1700-30	EA	21.00
	Consolidated Midland	0223-0667-02	EA	24.00
	AVERAGE COMMERCIAL PRICE			70.08

CHLORTHALIDONE TABLETS

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
	25 mg			
89	100's			
	Lederle	0005-3783-23	EA	1.56
	Rugby	0536-3486-01	EA	1.64
	Zenith	0172-2874-60	BT	1.60
	Barr	0555-0887-02	EA	1.67
	Mylan	0378-0222-01	BT	1.76
	US Trading	8011-382-01	EA	1.80
	Ponta	0630-0406-08	BT	1.82
	MLC	0832-0811-00	EA	1.90
	Schein	0364-0808-01	EA	1.94
	Bolar	0725-0083-01	EA	2.00
	Warner-Chilcott	0047-0123-24	BT	2.08
	Geneva	0781-172001	EA	2.12
	Jameson Pharm	50111-380-01	BT	2.13
	Pure Pac	0228-2161-10	BT	2.14
	Whitworth/TN Paulsen (Min order 12)	0157-0803-01	EA	2.20
	Whitworth/TN Paulsen	0157-0803-01	EA	2.27
	Goldline (12 or more)	0182-1434-01	EA	1.86
	Rowey (Min order 24)	0172-2874-60	EA	2.00
	Goldline	0182-1434-01	EA	2.50
	Baxter Healthcare (100s)	47679-314-01	BT	2.62
	Consolidated Midland	0223-0630-01	EA	3.86
	AVERAGE COMMERCIAL PRICE			6.06
90	250's			
	Consolidated Midland	0223-0630-25	EA	9.50
	AVERAGE COMMERCIAL PRICE			11.90
	50 mg			
91	100's			
	Rugby	0536-3488-01	EA	1.75
	Zenith	0172-2880-60	BT	1.95
	Lederle	0005-3784-23	EA	1.99
	Mylan	0378-0213-01	BT	2.05
	Schein	0364-0683-01	EA	2.06
	Barr	0555-0080-02	EA	2.25
	Ponta	0630-0408-08	BT	2.25
	MLC	0832-0812-00	EA	2.38
	US Trading	0885-0258-02	EA	2.44
	Pure Pac	0228-2163-10	BT	2.46
	Geneva	0781-172801	EA	2.50
	Vitarine	0185-0071-01	EA	2.50
	Baxter Healthcare (100s)	47679-315-01	BT	2.74
	Jameson Pharm	50111-383-01	BT	2.78
	Whitworth/TN Paulsen (Min order 12)	0157-0804-01	EA	2.87
	Whitworth/TN Paulsen	0157-0804-01	EA	2.95
	Rowey (Min order 24)	0172-2808-00	EA	3.20
	Warner-Chilcott	0047-0121-24	BT	3.27
	Goldline (12 or more)	0182-1436-01	EA	2.38
	Goldline	0182-1436-01	EA	3.78
	Consolidated Midland	0223-0631-01	EA	4.50
	AVERAGE COMMERCIAL PRICE			7.74
92	250's			
	Consolidated Midland	0223-0631-25	EA	9.95
	AVERAGE COMMERCIAL PRICE			15.88

CHLORZOXAZONE AND ACETAMINOPHEN, USP TABLETS

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
93	500's			
	Jameson Pharm	0003-0283-04	EA	10.20
	AVERAGE COMMERCIAL PRICE			66.76

CONTRACEPTIVES (ORAL) ETHINYL ESTRADIOL PREPARATIONS

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
94	With Norethindrone (Trade Agreement Act Applies)			
	Rugby (Min order 3)	0536-4088-44	EA	.84
	AVERAGE COMMERCIAL PRICE			(21's) 12.40
	AVERAGE COMMERCIAL PRICE			(28's) 12.42
95	With Norgestrel (Trade Agreement Act Applies)			
	Rugby (con eff 9/16/88)	0536-4085-46	EA	4.75

DIPHENHYDRAMINE HYDROCHLORIDE, USP (*SB Set-Aside)

ELIXIR

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
132	473 ml*			
	IDE	0814-2560-82	EA	1.87
	US Trading	0472-1227-16	EA	1.86
	MLC	50732-058-16	EA	1.88
	LuChem	50732-059-16	EA	1.91
	Halsey	0580-16	EA	2.00
	Jamesson Pharm	0472-1227-16	EA	2.40
	(12s)			
	AVERAGE COMMERCIAL PRICE			3.15

CAPSULES

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
	25 mg			
133	100's			
	Moore	00839-7458-06	EA	.98
	Penta	0839-1278-06	BT	.98
	Contract Pharmacal	10267-036-01	EA	1.02
	Whitworth/TN Poulson (Min order 12)	0157-0833-01	EA	1.07
	Whitworth/TN Poulson	0157-0833-01	EA	1.10
	Vitarine	0185-0648-01	EA	1.25
	Pure Pac	0228-2191-10	BT	1.31
	Barr	0555-0059-02	EA	1.33
	US Trading	0143-3136-01	EA	1.44
	Rugby	0536-3756-01	EA	1.51/c
	Kaye Pharm	0686-0062-02	BT	1.56
	Consolidated Midland	0223-0686-01	EA	1.75
	Baxter Healthcare (100s)	47679-474-01	BT	1.76
	Jamesson Pharm	0185-0007-01	BT	1.80
	AVERAGE COMMERCIAL PRICE			2.87

INJECTION, USP

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
	50 mg			
134	10 ml			
	Schein	0364-6839-54	EA	.90
	Steris	0402-0627-10	EA	1.06
	MLC	0402-0814-10	EA	1.08
	Moore	00839-6306-30	EA	1.22
	US Trading	0402-0814-10	EA	1.44
	Goldline (10 or more)	0182-3864-63	EA	1.46
	Goldline	0182-0864-63	EA	1.50
	Consolidated Midland	0223-7478-10	EA	2.10
	AVERAGE COMMERCIAL PRICE			5.60

DIPHENOXYLATE HYDROCHLORIDE W/ATROPINE SULFATE, USP TABLETS (*SB Set-Aside)

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
135	100's			
	US Trading	0143-1245-01	EA	1.24
	Barr	0555-0200-02	EA	1.33
	Halsey	0367-01	EA	1.46
	IDE	0814-2600-14	EA	1.50
	UDL	51079-067-40	EA	1.66
	Goldline (12 or more)	0182-1006-01	EA	1.30
	Goldline	0182-1006-01	EA	1.75
	West-Ward	0143-1245-01	EA	1.78
	Jamesson Pharm	0879-0367-01	BT	1.79
	Consolidated Midland	0223-0834-01	EA	3.50
	AVERAGE COMMERCIAL PRICE			5.02
136	1000's*			
	MD Pharm Inc	43567-526-12	EA	5.50
	Barr	0555-0200-05	EA	5.94
	US Trading	0143-1245-10	EA	6.44
	Mylan	0378-0415-10	BT	6.90
	MLC	0378-0415-10	EA	7.15
	Halsey	0367-10	EA	7.25
	UDL	51079-067-60	EA	7.44
	IDE	0814-2600-30	EA	7.87
	West-Ward	0143-1245-10	EA	8.36
	Goldline (6 or more)	0182-1006-10	EA	6.23
	Goldline	0182-1006-10	EA	8.98
	Jamesson Pharm	0879-0367-10	BT	9.38
	Consolidated Midland	0223-0834-02	EA	15.50
	AVERAGE COMMERCIAL PRICE			42.51

DIPRYDAMOLE TABLETS

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
	25 mg			
137	100's			
	Zenith	0172-2984-60	BT	1.00
	MLC	0832-1029-00	EA	1.00
	Penta	0839-6327-06	BT	1.10
	Barr	0555-0252-02	EA	1.13
	Geneva	0781-186001	EA	1.15
	Rugby	0536-3570-01	EA	1.18
	UDL	51079-068-40	EA	1.20
	Baxter Healthcare (100s)	47679-280-01	BT	1.20
	US Trading	49884-042-01	EA	1.24
	Lederle	0005-3743-23	EA	1.26
	Jamesson Pharm	52111-311-01	BT	1.30
	Whitworth/TN Poulson (Min order 12)	0157-0215-01	EA	1.33
	Whitworth/TN Poulson	0157-0215-01	EA	1.37
	Kaye Pharm	0686-0252-06	BT	1.46
	Goldline (12 or more)	0182-1156-01	EA	1.15
	Halsey	0457-01	EA	1.90
	Goldline	0182-1156-01	EA	1.50

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
	Schein	0364-0511-01	EA	1.84
	Rowey (Min order 24)	0172-2994-60	EA	1.75
	Consolidated Midland	0223-0837-01	EA	2.26
	AVERAGE COMMERCIAL PRICE			3.56
138	1000's			
	Barr	0555-0252-05	EA	6.21
	MLC	0832-1029-10	EA	6.30
	Best Generics (Max order 12)	0879-0494-10	EA	6.35
	Penta	0839-6327-16	BT	6.95
	Baxter Healthcare (1000s)	476780280-04	BT	6.86
	Geneva	0781-188010	EA	7.00
	Vangard	0615-1543-10	EA	7.12
	Jameson Pharm	50111-311-03	BT	7.54
	Kaye Pharm	0555-0252-05	BT	7.15
	Halsey	0497-10	EA	7.75
	Whiteworth/TN Paulsen (Min order 12)	0157-0215-10	EA	7.78
	US Trading	48884-042-10	EA	7.80
	Rugby	0536-3570-10	EA	7.86
	Whiteworth/TN Paulsen	0157-0215-10	EA	7.99
	UDL	51079-066-60	EA	8.80
	Goldline (6 or more)	0182-1196-10	EA	7.71
	Rowey (Min order 9.50)	0172-2994-80	EA	9.50
	Goldline	0182-1196-10	EA	9.50
	Schein (7 45/24)	0364-0511-02	EA	10.86
	Consolidated Midland	0223-0237-02	EA	20.75
	AVERAGE COMMERCIAL PRICE			20.75
139	2000's			
	AVERAGE COMMERCIAL PRICE			29.80
	50 mg			
140	100's			
	US Trading	48884-031-01	EA	1.22
	Zenith	0172-2976-60	BT	1.70
	MLC	0832-1030-00	EA	1.70
	Barr	0555-0286-02	EA	1.72
	Penta	0839-6404-06	BT	2.02
	Geneva	0781-167801	EA	2.10
	Kaye Pharm	0555-0286-02	BT	2.10
	Halsey	0479-01	EA	2.10
	Rugby	0536-3571-01	EA	2.20
	Lederle	0005-3790-23	EA	2.21
	Baxter Healthcare (100s)	47679-440-01	BT	2.40
	Jameson Pharm	50111-313-01	BT	2.55
	Whiteworth/TN Paulsen (Min order 12)	0157-0216-01	EA	2.63
	UDL	51079-069-40	EA	2.64
	Goldline (12 or more)	0182-1405-01	EA	2.15
	Whiteworth/TN Paulsen	0157-0216-01	EA	2.70
	Schein	0364-0586-01	EA	2.73
	(2.90/24)			
	Rowey (Min order 24)	0172-2976-60	EA	2.75
	Goldline	0182-1405-01	EA	2.75
	Consolidated Midland	0223-0838-01	EA	5.50
	AVERAGE COMMERCIAL PRICE			6.97
141	500's			
	Barr	0555-0286-04	EA	7.16
	Zenith	0172-2976-70	BT	7.25
	Lederle	0005-3790-31	EA	8.53
	Kaye Pharm	0555-0286-04	BT	8.75
	US Trading	48884-031-05	EA	9.44
	Rugby	0536-3571-05	EA	9.95
	Jameson Pharm	0172-2976-70	EA	10.34
	Rowey (Min order 24)	0172-2976-70	EA	11.00
	Consolidated Midland	0223-0838-05	EA	19.50
	AVERAGE COMMERCIAL PRICE			27.96
142	1000's			
	MLC	0832-1030-10	EA	11.96
	Best Generics (max order 12)	0879-0479-10	EA	13.80
	Halsey	0479-10	EA	14.75
	Penta	0839-6404-16	BT	14.95
	Rugby	0536-3571-10	EA	14.95
	Geneva	0781-167810	EA	15.20
	Vangard	0615-1573-10	EA	15.50
	US Trading	48884-031-10	EA	15.75
	Jameson Pharm	50111-313-03	BT	16.32
	Whiteworth/TN Paulsen (Min order 12)	0157-0216-10	EA	16.80
	Whiteworth/TN Paulsen	0157-0216-10	EA	17.30
	Goldline (6 or more)	0182-1405-10	EA	16.97
	UDL	51079-069-60	EA	17.50
	Goldline	0182-1405-10	EA	17.96
	Schein	0364-0586-02	EA	18.13
	Rowey (Min order 24)	0172-2976-80	EA	19.00
	Consolidated Midland	0223-0838-02	EA	37.50
	AVERAGE COMMERCIAL PRICE			39.94
	75 mg			
143	100's			
	MLC	0832-1031-00	EA	2.38
	Zenith	0172-2977-60	BT	2.40
	US Trading	48884-065-01	EA	2.50
	Rugby	0536-3573-01	EA	2.52
	Penta	0839-6420-06	BT	2.71
	Geneva	0781-147801	EA	2.75
	Barr	0555-0288-02	EA	2.80
	Lederle	0005-3791-23	EA	2.84
	Baxter Healthcare (100s)	47679-313-01	BT	2.98
	UDL	51079-070-40	EA	3.13
	Halsey	0467-01	EA	3.15
	Rowey (Min order 24)	0172-2977-60	EA	3.40
	Jameson Pharm	50111-313-01	BT	3.43

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
	Schein (Foreign)	0364-0892-01	EA	5 83
	Geneva	0781-235001	TU	4 88
	Whitworth/TN Paulsen	0157-0983-01	EA	5.71
	(Min order 12)			
	Jameson Pharm	52544-304-01	BT	5 78
	Kaye Pharm	0555-0337-02	BT	5 86
	Whitworth/TN Paulsen	0157-0983-01	EA	5 87
	MLC	0378-0147-01	EA	6 05
	Baxter Healthcare	47679-537-01	BT	7 61
	(100)			
	Consolidated Midland	0223-1090-01	EA	9 50
	Goldline	0182-1882-01	EA	4 90
	(12 or more)			
	Goldline	0182-1882-01	EA	10 50
	AVERAGE COMMERCIAL PRICE			23 91
231	500's			
	US Trading	0555-0337-04	EA	12 50
	US Trading	49884-088-05	EA	12 50
	US Trading	51285-276-04	EA	12 90
	Barr	0555-0337-04	EA	16 50
	(Foreign)			
	Halsey	0508-05	EA	16 50
	Lederle	0005-3782-31	EA	16 82
	Zenith	0172-4030-70	BT	13 26
	Best Generics	54274-122-30	EA	19 84
	(Min order 12)			
	Mylan	0378-0147-05	BT	20 00
	Rugby (Foreign)	0536-3882-05	EA	18 60
	Schein (Foreign)	0364-0882-05	EA	24 86
	Geneva	0781-235005	TU	22 68
	Whitworth/TN Paulsen	0157-0883-05	EA	26 86
	(Min order 12)			
	Kaye Pharm	0555-0337-04	BT	26 96
	Jameson Pharm	52544-304-05	BT	27 00
	Whitworth/TN Paulsen	0157-0883-05	EA	27 46
	MLC	0378-0147-05	EA	28.06
	Goldline	0182-1882-05	EA	22 96
	(6 or more)			
	Goldline	0182-1882-05	EA	41.96
	Consolidated Midland	0223-1096-05	EA	47.50
	AVERAGE COMMERCIAL PRICE			80 10

ISONIAZID TABLETS

100 mg

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
232	100's			
	Rugby	0536-3848-01	EA	96
	Halsey	0113-01	EA	96
	Jameson Pharm	0186-4351-01	BT	1.04
	Vitarine	0186-4351-01	EA	1.10
	Whitworth/TN Paulsen	0157-0865-01	EA	1.19
	(min order 12)			
	Whitworth/TN Paulsen	01577-0865-01	EA	1.22
	Bolar	0725-2150-01	EA	1.25
	Barr	0555-0066-02	EA	1.25
	(Foreign)			
	Consolidated Midland	0223-1150-01	EA	1.25
	Geneva	0781-125801	TU	1 28
	West-Ward	0143-1260-01	EA	1.36
	AVERAGE COMMERCIAL PRICE			2 34
233	1000's			
	Schein	0364-0150-02	EA	4 36
	Vitarine	0186-4351-10	EA	4 15
	Geneva	0781-125810	TU	4 20
	West-Ward	0143-1260-05	EA	4 94
	Bolar	0725-2150-10	EA	5 50
	Jameson Pharm	0185-4351-10	BT	5 57
	Halsey	0113-10	EA	5 75
	Whitworth/TN Paulsen	0157-0865-10	EA	5 85
	(Min order 12)			
	Whitworth/TN Paulsen	0157-0865-10	EA	5 90
	Rugby	0536-3848-10	EA	6 75
	Barr	0555-0066-05	EA	7 30
	(Foreign)			
	Consolidated Midland	0223-1150-02	EA	9 50
	Goldline	0182-0580-10	EA	7 29
	(12 or more)			
	Goldline	0182-0588-10	EA	9 99
	AVERAGE COMMERCIAL PRICE			12 58

ISOSORBIDE DINITRATE, USP TABLETS

10 mg

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
234	100's			
	Geneva	0781-158801	TU	0 75
	Schein	0364-0341-01	EA	87
	US Trading	0555-0175-02	EA	90
	US Trading	49884-021-01	EA	90
	Rugby	0536-3843-01	EA	90
	Barr	0555-0175-02	EA	1 05
	(Foreign)			
	Baxter Healthcare	47679-237-01	BT	1 09
	(100s)			
	Best Generics	0555-0175-02	EA	1 19
	(Min order 24)			
	Goldline	0182-0514-01	EA	96
	(12 or more)			
	Penta	0629-1381-04	BT	1 35
	Jameson Pharm	0555-0175-02	BT	1 36
	Goldline	0182-0514-01	EA	1.39
	Consolidated Midland	0223-1086-01	EA	1 50
	West-Ward	0143-1771-01	EA	1 89
	AVERAGE COMMERCIAL PRICE			3 24
235	Unit Dose/100's			
	Vangard	0615-1580-13	EA	1 66
	UDL	51079-029-20	EA	1 96
	Baxter Healthcare	47679-237-36	BX	1 97
	(100s)			
	Geneva	0781-158813	EA	2.69
	US Trading	0615-1580-13	EA	2 90
	US Trading	0143-1771-35	EA	2 99
	West-Ward	0143-1771-35	EA	3 42
	Jameson Pharm	0143-1771-35	EA	4 26
	Consolidated Midland	0223-1086-06	EA	4 96
	AVERAGE COMMERCIAL PRICE			6 50

20 mg

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
	AVERAGE COMMERCIAL PRICE		PIN TOP	2.16
	Abbott (add-syr)	0074-4902-01	EA	2.18
	AVERAGE COMMERCIAL PRICE		PPTV	3.09
383	44 mEq/50 ml			
	Lypho-Med	0469-2087-15	VL	26
	Abbott (l-top)	0074-6653-05	EA	.5262
	AVERAGE COMMERCIAL PRICE		AMP	0.54
	Jamesen Pharm (25s)	0467-0520-15	EA	57
	AVERAGE COMMERCIAL PRICE		VI	0.63
	Consolidated Midland (100's)	0223-6331-10	EA	63
	Abbott (p-top)	0074-4938-01	EA	1.08
	AVERAGE COMMERCIAL PRICE		PINTOP	1.820
	Abbott (add-syr)	0074-4904-01	EA	2.63
	AVERAGE COMMERCIAL PRICE		SYRINGE	5.24
384	50 mEq/50 ml			
	Lypho-Med	0469-0067-15	VI	58
	AVERAGE COMMERCIAL PRICE		VL	0.67
	Consolidated Midland (25's)	0223-6332-30	EA	67
	AVERAGE COMMERCIAL PRICE		MDV	0.70

POVIDONE-IODINE USP SOLUTION (*SB Set-Aside)

1%

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
385	237 ml			
	Sherwood (Case 12.40)	12772-177-25	BT	62
	Thatcher Co	038032-390-06	EA	675
	Rexall	0369-0169-06	EA	93
	Schein	0364-7202-76	EA	1.12
	AVERAGE COMMERCIAL PRICE			1.42
386	473 ml			
	Sherwood (Case 11.40)	12772-177-30	BT	95
	Thatcher Co	038032-390-16	EA	96
	Moore	00839-6914-69	EA	2.00
	IDE	0814-6236-68	EA	2.06
	US Trading	0472-1406-16	EA	2.22
	Consolidated Midland	0223-6641-01	EA	2.95
	AVERAGE COMMERCIAL PRICE			2.56
387	946 ml			
	Sherwood (Case 22.30)	12772-177-16	BT	1.86
	Thatcher Co	038032-390-32	EA	1.99
	Rexall	0369-0169-32	EA	2.90
	AVERAGE COMMERCIAL PRICE			2.85

POVIDONE-IODINE SCRUB USP

7.5%

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
388	473 ml			
	Sherwood (Case 12.48)	12772-186-60	BT	1.04
	Thatcher Co	038032-186-16	EA	1.085
	Rexall	0369-0177-16	EA	1.47
	Schein	0364-7203-16	EA	1.63
	Best Generics (Min order 6)	0472-1407-16	EA	1.94
	Parmed	0839-6914-69	EA	1.99
	US Trading	0472-1407-16	EA	2.19
	Rugby	0536-1826-85	EA	2.30
	Goldline (12 or more)	0182-0786-40	EA	2.07
	Consolidated Midland	0223-6640-01	EA	2.45
	Goldline	0182-0786-40	EA	2.46
	AVERAGE COMMERCIAL PRICE			2.46
389	3.78 Liter			
	Thatcher Co	038032-186-26	EA	6.71
	Sherwood (Case 28.76)	12772-186-10	BT	7.19
	Rexall	0369-0177-28	EA	9.20
	Rugby	0536-1826-60	EA	10.75
	US Trading	0472-1407-26	EA	11.75
	Goldline (4 or more)	0182-0786-41	EA	11.96
	Consolidated Midland	0223-6640-02	EA	12.45
	Goldline	0182-0786-41	EA	12.53
	AVERAGE COMMERCIAL PRICE			12.53

PREDNISONE TABLET USP *(SB Set-Aside)

5 mg

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
390	1000's			
	Whiteworth/Tn Paulsen (Min order 12)	0157-0824-10	EA	7.30
	Whiteworth/Tn Paulsen	0157-0824-10	EA	7.52
	Parmed	0839-5143-16	BT	8.20
	Geneva	0781-148810	TU	8.25
	Moore	00839-5143-16	EA	8.85
	Halsey	0129-10	EA	8.95
	Roxane Rowell 9.46/M	0033-2810-10	EA	9.46
	IDE	0814-6295-30	EA	9.46
	Jamesen Pharm	50349-141-10	BT	10.04
	West-Ward	0143-1475-10	EA	10.07
	Goldline (6 or more)	0182-0301-10	EA	8.31
	Goldline	0182-0301-10	EA	10.99
	Consolidated Midland	0223-1615-02	EA	12.86
	AVERAGE COMMERCIAL PRICE			15.97

10 mg

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
391	100's			
	Whiteworth/Tn Paulsen (Min order 12)	0157-0813-01	EA	1.89
	Whiteworth/Tn Paulsen	0157-0813-01	EA	1.95
	Geneva	0781-189001	TU	1.98
	Schein	0364-0461-01	EA	2.19
	Pure Pac	0228-2336-10	BT	2.20
	Roxane	0054-4730-25	BT	2.24
	Rugby	0536-4325-01	EA	2.25

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
	Consolidated Midland	0223-1465-01	EA	6.90
	AVERAGE COMMERCIAL PRICE			6.23

PROPOXYPHENE HYDROCHLORIDE CAPSULES, USP (*SB Set-Aside)

65 mg

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
308	100's			
	Geneva	0781-214001	TU	2.20
	Best Generics (Min order 24)	0879-0155-01	EA	2.28
	Rugby	0536-4362-01	EA	2.40
	Moore	00839-5086-06	EA	2.50
	Penta	0839-5086-06	BT	2.50
	Schein	0364-0213-01	EA	2.81
	Lederle	0005-4547-23	EA	2.92
	Halsey	0155-01	EA	2.95
	US Trading	0143-3235-01	EA	2.95
	Jameson Pharm	0143-3235-01	EA	3.14
	Pure Pac	0228-2062-10	BT	3.30
	Goldline	0182-0666-01	EA	2.99
	(12 or more)			
	Goldline	0182-0666-01	EA	3.05
	Jameson Pharm	0143-3235-01	EA	3.14
	Consolidated Midland	0223-1530-01	EA	6.90
	AVERAGE COMMERCIAL PRICE			5.92
309	500's			
	Moore	00839-5086-12	EA	10.56
	Halsey	0155-05	EA	10.95
	Penta	0839-5086-12	BT	10.95
	Jameson Pharm	0143-3235-05	EA	11.77
	IDE	0814-6407-30	EA	12.37
	US Trading	0143-3235-05	EA	13.95
	Consolidated Midland	0223-1560-05	EA	27.50
	AVERAGE COMMERCIAL PRICE			26.20

PROPRANOLOL HCL TABLETS

20 mg

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
310	100's			
	Lederle	0005-3110-23	EA	.76
	Pure Pac	0228-2329-10	BT	1.02
	Geneva	0781-136401	TU	1.10
	Mylan	0378-0183-01	BT	1.10
	Rugby	0536-4313-01	EA	1.18
	US Trading	49884-107-01	EA	1.25
	Barr (Foreign)	0555-0360-02	EA	1.30
	Schein	0364-0737-01	EA	1.31
	MLC	0378-0183-01	EA	1.38
	Roxane	0054-4730-25	BT	1.40
	Pro-Cute	53000-074-01	BT	1.45
	Whitworth/Tn Paulsen (Min order 12)	0157-6027-01	EA	1.57
	Jameson Pharm	52544-395-01	BT	1.59
	Whitworth/Tn Paulsen	0157-6027-01	EA	1.62
	Kaye Pharm	0555-0360-02	BT	1.75
	Warner-Chilcott	0047-0071-34	BT	1.37
	Goldline	0182-1759-01	EA	1.85
	(12 or more)			
	Goldline	0182-1759-01	EA	2.45
	Penta	0839-7116-06	BT	2.95
	Consolidated Midland	0223-1436-01	EA	3.25
	AVERAGE COMMERCIAL PRICE			11.56

40 mg

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
311	100's			
	Lederle	0005-3111-23	EA	1.18
	Pure Pac	0228-2331-10	BT	1.26
	Barr (Foreign)	0555-0367-02	BT	1.40
	Mylan	0378-0184-01	BT	1.45
	Rugby	0536-4314-01	EA	1.46
	US Trading	49884-108-01	EA	1.50
	Roxane	0054-4789-25	BT	1.54
	Pro-Cute	53000-075-01	BT	1.60
	MLC	0378-0184-01	EA	1.71
	Geneva	0781-136401	TU	1.75
	Schein	0364-0758-01	EA	1.75
	Warner-Chilcott	0047-0072-34	BT	1.78
	Whitworth/Tn Paulsen (Min order 12)	0157-6526-01	EA	2.40
	Jameson Pharm	52544-397-01	BT	2.43
	Whitworth/Tn Paulsen	0157-6526-01	EA	2.47
	Kaye Pharm	0555-0367-02	BT	2.70
	Penta	0839-7116-06	BT	3.20
	Goldline	0182-1760-01	EA	1.67
	(12 or more)			
	Goldline	0182-1760-01	EA	3.75
	Consolidated Midland	0223-1436-01	EA	6.25
	AVERAGE COMMERCIAL PRICE			15.69

PSEUDEOPHEDRINE HYDROCHLORIDE, USP (SB Set-Aside)

60 mg

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
312	1000's			
	OHM Labs*	51660-076-10	EA	7.75
	Moore	00839-1543-16	EA	8.06
	Halsey	0425-10	EA	8.75
	West-Ward	0143-1485-10	EA	8.86
	Invamed	52189-110-30	EA	9.00
	Penta	0839-1543-16	BT	9.00
	Geneva	0781-152016	TU	9.12
	Contract Pharmacal	10267-1016-10	EA	9.50
	Goldline	0182-0513-10	EA	16.31
	(6 or more)			
	Goldline	0182-0513-10	EA	10.60
	Jameson Pharm	0879-0475-10	EA	10.60
	IDE	0814-6407-30	EA	11.62
	Consolidated Midland	0223-1475-02	EA	13.60
	AVERAGE COMMERCIAL PRICE			14.21

QUINDINE GLUCONATE TABLETS SUSTAINED RELEASED

324 mg

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
313	250's			
	Berlex Labs	50419-101-25	EA	25.00
	Bolar	0735-3000-60	EA	25.00

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
	Geigy (CD)	0028-0105-80	EA	46.78
	AVERAGE COMMERCIAL PRICE			280.26
332	Unit Dose/100's			
	Geigy Pharm	0028-0105-61	EA	6.45
	AVERAGE COMMERCIAL PRICE			21.27

TETRACYCLINE HYDROCHLORIDE USP CAPSULES

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
	250 mg			
333	100's			
	Squibb	0003-0655-10	EA	1.87
	Parke	0029-1050-00	BT	1.91
	Zenith	0172-2410-60	BT	1.96
	Rugby	0536-1820-01	EA	2.09
	Vitarine	0185-0670-01	EA	2.10
	Schein	0364-2027-01	EA	2.12
	Warner-Chilcott	0047-0407-24	BT	2.15
	Pure Pac	0228-2404-10	BT	2.28
	Best Generics (Min order 24)	0089-0011-02	EA	2.34
	Lederle	0005-4069-23	EA	2.40
	Halsey	0199-01	EA	2.50
	Goldline (12 or more)	0182-0112-01	EA	2.21
	US Trading	0056-001-02	EA	2.75
	Goldline	0182-0112-01	EA	2.75
	Jameson Pharm	0172-2410-60	EA	2.78
	Consolidated Midland	0223-1060-01	EA	3.90
	AVERAGE COMMERCIAL PRICE			4.34
334	1000's			
	NO AWARD			
	500 mg			
335	100's			
	Parke	0029-5075-09	BT	3.06
	Geneva	0781-240001	TU	3.16
	Zenith	0172-2407-60	BT	3.20
	Squibb	0003-0763-40	EA	3.20
	Lederle	0005-4075-23	EA	3.20
	Rugby	0536-1870-01	EA	3.25
	Barr (Foreign)	0555-0016-02	EA	3.30
	Schein	0364-2209-01	EA	3.38
	Wyeth Labs	0008-0471-01	EA	3.51
	Halsey	0199-01	EA	3.75
	MLC	0075-0100-01	EA	3.01
	Best Generics (Min order 24)	0056-0010-02	EA	4.07
	Pure Pac	0228-2406-10	BT	4.13
	Goldline (12 or more)	0182-0070-01	EA	3.82
	Jameson Pharm	0056-0010-02	BT	4.21
	Goldline	0182-0070-01	EA	4.25
	US Trading	0056-0011-02	EA	4.44
	Consolidated Midland	0223-1060-01	EA	6.59
	AVERAGE COMMERCIAL PRICE			6.83
336	1000's			
	NO AWARD			
	500 mg			

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
337	Injection			
	Lederle	0005-4771-60	EA	7.25
	AVERAGE COMMERCIAL PRICE			14.51

THEOPHYLLINE TABLETS

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
	200 mg			
338	100's			
	3M Riker	0089-0341-10	EA	2.30
	Parke	0029-0720-00	BT	7.10
	Best Generics (min order 24)	0256-3583-01	EA	7.46
	US Trading	0056-3583-01	EA	7.77
	Jameson Pharm	0056-3583-01	EA	8.30
	Schein	0364-0661-01	EA	8.25
	Goldline (12 or more)	0182-1060-01	EA	7.99
	Goldline	0182-1060-01	EA	9.95
	AVERAGE COMMERCIAL PRICE			10.41
339	Unit Dose/100's			
	US Trading	0143-1069-25	EA	11.11
	Jameson Pharm	0143-1069-25	EA	13.12
	AVERAGE COMMERCIAL PRICE			18.24
	300 mg			
340	Unit Dose 100's			
	3M Riker	0089-0343-10	EA	3.20
	Best Generics (Min order 24)	0256-3581-01	EA	9.60
	US Trading	0256-3581-01	EA	9.95
	Schein	0364-0660-01	EA	10.61
	Goldline (12 or more)	0182-1460-01	EA	10.34
	Goldline	0182-1460-01	EA	12.50
	AVERAGE COMMERCIAL PRICE			14.44
341	Unit Dose 100's			
	US Trading	0143-1069-25	EA	12.13
	AVERAGE COMMERCIAL PRICE			14.08

THIAMINE HYDROCHLORIDE USP TABLETS

Index No.	Description/ Quantity Contractor	National Drug Code	Unit of Issue	Price ($) Each
	100 mg			
342	Unit Dose/100's			
	Baxter Healthcare (100's)	47679-126-35	BX	1.96
	Goldline Labs	0182-0047-89	EA	2.00
	Vangard	0615-0597-13	EA	2.08
	UDL	51079-014-20	EA	2.30
	Pro-Care (10 x 10)	00999-138-75	EA	2.44
	US Trading	0143-1729-25	EA	2.85
	US Trading	0615-0597-13	EA	2.89
	West-Ward	0143-1729-25	EA	2.90
	Consolidated Midland	0223-2949-60	EA	2.95
	Jameson Pharm	0143-1729-25	EA	3.54
	Rowey (Min order 24)	0615-0597-13	EA	3.75

QUESTION NUMBER 2:

In general, what is magnitude of discounts realized by VA (expressed as a percentage of the Average Wholesale Price published in the U.S. at the time of DVA's purchase) as a result of its negotiations with manufacturers for procurement of (a) multiple source and (b) single source prescription drugs?

ANSWER TO QUESTION NUMBER 2:

Generally the Department of Veterans Affairs obtains discounts averaging 41% for single source prescription drugs and 67% for multiple source drugs when measured against Average Wholesale Price. These prices represent the cost to a federal customer through commercial distribution channels and not drugs owned and distributed by the Government.

For the drugs identified as depot stocked, the single source pharmaceutical products vary in discount from Average Wholesale Price with a low discount of 22% and the best discount of 90%. The variance is based on the manufacturer's pricing policies and willingness to negotiate for a market they possess. For multiple source drugs discounts range from 39% to 93%, but most multiple source drugs are currently being purchased with discounts of greater than 80% from Average Wholesale Price.

QUESTION NUMBER 3:

During the period 1981 - 1988, what has been the approximate annual rate of increase in prices paid by DVA for those prescription drugs purchased through negotiations with drug manufacturers?

ANSWER TO QUESTION NUMBER 3:

The cost of drugs from 1981 to the present can only be tracked for items in our depot distribution system. It is difficult to generalize the trend in cost as a firm increase or decrease because variables such as competition have a dramatic effect. It is relatively safe to identify single source drugs as increasing annually. Multiple source drugs have declined in the depot system an average of 51.7% below prices that were paid in 1981.

QUESTION NUMBER 4:

Does DVA sometimes find it necessary to purchase prescription drugs at prices which are not negotiated with the drug manufacturer? If so, please indicate the reasons and/or cicumstances under which DVA would purchase a prescription drug at a non-negotiated price, and the price paid (or basis for establishing the price paid) by DVA for prescription drugs under these circumstances.

ANSWER TO QUESTION NUMBER 4:

The individual VA Medical Centers do on occasion purchase drugs and pharmaceuticals at non contract prices. Most often this is the result of an emergency requiring a local purchase from the nearest wholesaler to satisfy the critical need that has generated the action. Pricing under these conditions may result in a cost to the pharmacy as high as 300-400% greater than depot or Federal Supply Schedule cost for the same drug.

QUESTION NUMBER 5:

What problems has the DVA encountered in attempting to negotiate favorable prices with manufacturers of multiple source and single source drugs? How has DVA attempted to resolve these problems?

ANSWER TO QUESTION NUMBER 5:

The single problem encountered in negotiating with manufacturers generally relates to the market share Department of Veterans Affairs Medical Centers represent. A decade ago, VA was 1 of the 5 largest customers to the pharmaceutical industry. Today, due to the consortia, buying groups and Health Maintenance Organizations, it is not even among the 10 largest buying organizations in the United States for drugs and pharmaceutical products.

The most adverse situation we face is the select group of manufacturers choosing not to enter into either a Federal Supply Schedule or provide their proprietary items to the Department for depot stock.

QUESTION NUMBER 6:

In preparing for or conducting negotiations with prescription drug manufactures, does DVA utilize information on prices paid by other governmental purchasers of prescription drugs products (a) in the United States and (b) by foreign governments? Would such information be useful to DVA in its negotiations?

ANSWER TO QUESTION NUMBER 6:

In preparation for single source drug negotiations, we obtain as much information as possible concerning the current pricing of the drugs for which we are contracting. This is accomplished by reviewing commercial publications such as the "Drug Topics Redbook" and a monthly publication which provides updates on brand name prices from "Medispan". We also review the current Producer Price Index and prior year pricing as a minimum to prepare ourselves for negotiation. Generic drugs are reviewed the same way, but there is no question that the existence of competition is the driving force in negotiating the best prices for generics. Market awareness and price analysis confirm the reasonableness of the contract award, but, if the offerors were not in direct price competition, the Department of Veterans Affairs would be in a less advantageous position. The Waxman Hatch Act has had a positive influence in stimulating the introduction of generic drugs and the effect is very noticeable. Competition and large volume are the keys to favorable prices. Our negotiations are always carried out with the best interest of the Government in mind while recognizing the need for a "win/win" end result.

The Department of Veterans Affairs negotiates and manages its Federal Supply Schedules for drugs and Pharmaceuticals under the format prescribed by the General Services Administration. Obtaining a Federal Supply Schedule contract for a proprietary product line on a multiple award schedule requires the disclosure of discounting practices for all classes of trade. Bidders complete a Discount Schedule and Marketing Data section of the solicitation with this information. We have developed a computer program which performs a price analysis of the drugs and compares the Government's position to the "most favored customer" supplied by the offeror. It also determines a negotiation objective for Government based on the analysis and prices offered other customers. The use of this program has enhanced our ability to negotiate under the Federal Supply Schedule and obtain better pricing for the Federal customer.

Our generic drug Federal Supply Schedule identifies the specific items we intend to have under contract. Offerors provide a price only. Since no disclosure data exists, we determine an average commercial price from all suppliers identified through the "Redbook". This represents the maximum price determined reasonable for Government, and negotiations are conducted with suppliers to obtain an equal to or better price. If this is attained, the item is awardable. If not, no award is made to that supplier. Our Federal Supply Schedule assignments are of the multiple award type because there are subtle differences even in therapeutic equivalent drugs. Buffering agents and tablet compression can be variables that are not addressed by the compendia.

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United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

June 6, 1989

Mr. Gordon Binder
Chief Executive Officer
Amgen, Inc.
1900 Oak Terrace
Newberry Park, CA 91320

Dear Mr. Binder:

On Thursday, June 22, 1989, the Senate Special Committee on Aging will convene a hearing on the subject of prescription drug manufacturer pricing policies and practices. I would like to take this opportunity to invite you to appear before the Committee to testify on this subject. I also request that you provide the Committee with materials, described below, which will assist us in our examination of this important issue.

This hearing will examine factors contributing to prescription drug cost increases in recent years, and explore opportunities in the current marketplace for third party payors, service providers and others to negotiate prescription drug purchase prices with manufacturers. Examples of negotiated prices of interest to the Committee include price discounts afforded by manufacturers to government agencies, such as the Veterans' Administration and Department of Defense, and to health care providers and buying groups, including hospitals, Health Maintenance Organizations, and retail pharmacies.

You or your representative's testimony should provide answers, accompanied by relevant data and information requested below, to the following specific questions:

1. What potential benefits does your new drug, Epogen, offer for Medicare beneficiaries? What health care costs might be reduced or eliminated for beneficiaries with specific ailments or disabilities, if they were to begin using Epogen as part of their treatment regimen?

2. Recent news reports (e.g., Washington Post, June 2, 1989, p.1) indicate that it costs approximately $140 to manufacture a typical patient's one year supply of your firm's new product Epogen, while the retail price of such a supply will range from $4,000 to $8,000 per year. Reports also note that your firm spent $100 million developing Epogen and that Medicare will annually incur $200-500 million insuring kidney dialysis patients who use the product. Please confirm or correct this information in your testimony.

3. In the course of its clinical testing, was Epogen tested in a substantial number of elderly subjects? What special considerations pertaining to the elderly user, if any, were found to be appropriate in the course of these trials? Does Epogen's product labeling contain a special section advising the physician on use in the elderly population?

4. What is the amount of money spent by your firm on prescription drug research and development in each year from 1981 through 1988?

5. For each year from 1981 through 1988, what is the amount of tax savings received by your firm for prescription drug research and development pursuant to Section 41 of the Internal Revenue Code, pertaining to qualified research expenses?

— —

6. Has your firm sold its prescription drug products to foreign or U.S. government agencies which involve price discounts below the Average Wholesale Price (AWP) published in the U.S. at the time of sale? Which foreign and U.S. government agencies have been involved in such sales, and what have been the specific discounts (expressed as a percentage of the AWP) involved in each such sale during calendar years 1988 and 1989?

7. Has your firm entered into agreements to sell its prescription drug products to domestic or foreign third party payors (other than government agencies) involving price discounts below the AWP published in the U.S. at the time of sale? If so, what was the range of discounts (expressed as a percentage of the AWP) agreed to pursuant to such agreements during the calendar years 1988 and 1989? (Your firm will not be asked to publicly name other parties to these agreements.)

8. Has your firm sold its prescription drug products to foreign or domestic health care providers, including buying groups representing providers, at price discounts below the AWP published in the U.S. at the time of sale? If so, please furnish a description of the type(s) of providers or groups which have purchased prescription drug products from your firm at a discount below the published U.S. AWP, as well as the range of discounts (expressed as a percentage of the AWP) associated with such sales to each identified type of provider or group during calendar years 1988 and 1989. (Your firm will not be asked to publicly name other parties to such sales.)

In addition, please provide copies of all materials concerning identification and price data of patented medicines, if any, that were submitted by your firm to the Canadian Patented Medicines Review Board in 1988 and 1989 pursuant to Sections 3 and 4 of the Regulations promulgated under Section 4(1)(i) of the Canadian Patent Act. Please be certain that these materials, if any, include (a) your firm's price lists for the Federal Republic of Germany, France, Italy, Sweden, Switzerland, United Kingdom, United States, and Canada, and (b) data regarding actual transactions in Canada. It would be greatly appreciated if these materials, previously compiled for and submitted to the Canadian government, are delivered to the Committee office no later than close of business on June 12, 1989.

The Committee's hearing is scheduled to begin at 9:30 a.m. in room SD-562 of the Dirksen Senate Office Building. I would very much appreciate your providing the Committee with ten copies of your written testimony by close of business on June 19, and an additional 100 copies on the morning of June 21, 1989. Your testimony for submission into the record may be of whatever length you deem appropriate. The Committee would, however, appreciate your limiting oral remarks to no more than five minutes.

Thank you for your cooperation and assistance in this inquiry by the Committee. Should you have questions relating to this invitation and request for information, please have your staff contact David Schulke of the Special Committee on Aging staff at 202-224-5364.

Sincerely,

David Pryor

David Pryor
Chairman

DP:dgs

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United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

June 14, 1989

Mr. Gerald J. Mossinghoff
President
Pharmaceutical Manufacturers' Association
1100 Fifteenth Street, N.W.
Washington, D.C. 20005

Dear Mr. Mossinghoff:

Thank you for your letters of May 25 and June 5, 1989, in which you requested an opportunity for the Pharmaceutical Manufacturers' Association (PMA) to present testimony to the Special Committee on Aging regarding prescription drug pricing policies of drug manufacturers. We appreciate your willingness to assist the Committee in its inquiry, and would like to thank the Association for the cooperation its staff has already extended.

We have thought carefully about your request to present oral testimony at the Committee's hearing. As Members of the Committees on Aging, Finance, and Governmental Affairs, we have often appreciated the value of association testimony on behalf of an industry affected by governmental policy. Association testimony is particularly effective in conveying points of agreement between and among the varied interests and factions that inevitably exist in any industry. The Special Committee on Aging, however, has a special role in that our investigative hearings are designed to develop and establish facts based on original sources and evidence. For this Committee, identifying the priorities and common concerns hammered out within a particular industry or trade group -- of critical importance to authorizing committees' allocation of resources through the budgetary process -- is secondary to our fact-finding function. In evaluating your request, therefore, we viewed the following considerations as being of paramount importance.

Pricing strategies are not determined on an industry-wide basis but are highly specific to individual firms. Indeed, firms' strategies are frequently quite divergent. Accordingly, the Committee has requested data directly from manufacturers, and has called this hearing so Members can ask relevant questions of those responsible for determining company policies and procedures pertaining to pricing of prescription drug compounds.

Mr. Gerald J. Mossinghoff
June 14, 1989
Page 2

The Association, in contrast with its member firms, lacks specific knowledge of firms' pricing policies, or the reasons behind these decisions, and is prohibited by anti-trust statutes from participating in price-setting. Inasmuch as the Association is neither responsible nor accountable for manufacturers' decisions with respect to pricing of prescription drugs, we believe the Committee's limited hearing time will be most fruitfully employed in frank dialogue with company decision-makers, based on actual pricing data.

We are mindful that several firms have expressed their desire for the Association to be represented at the hearing. With the aim of providing invited firms every incentive to participate in this hearing, we are prepared to accept PMA's oral testimony. We are not prepared, however, to accept PMA's testimony in lieu of the participation of the invited manufacturers themselves. Accordingly, we would appreciate the Association making every effort to encourage its members to cooperate fully with the Committee, both by providing requested data and by testifying before the Committee.

Your oral remarks will be limited to no more than five minutes, but the Association's written statement may be of whatever length you deem appropriate. If 150 copies of written testimony are received in the Committee office by June 19, it will be distributed in the Committee's press packets on the day of the hearing.

Thank you for your interest in the Committee's examination of prescription drug manufacturer pricing practices. We hope that we can count on your continued assistance, particularly in encouraging member firms to cooperate fully with the Committee in its inquiry.

Sincerely,

David Pryor
David Pryor
Chairman

John Heinz
John Heinz
Ranking Member

DP/JH:ds

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United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

June 20, 1989

Mr. Gordon Binder
Chief Executive Officer
Amgen, Inc.
1900 Oak Terrace
Newberry Park, CA 91320

Dear Mr. Binder:

I am writing in regard to the hearing on prescription drug pricing that will be held by the Special Committee on Aging. Since my letter of invitation and request for information, several invited manufacturer executives have written to me, declining to appear before the Committee on June 22nd because of scheduling conflicts.

As Committee staff indicated to the Pharmaceutical Manufacturers Association yesterday, in recognition of these firms' scheduling difficulties I have elected to reschedule the hearing to mid-July 1989. Shortly you will receive an invitation for a new hearing date that I hope executives will find more convenient.

I also have received from several firms the suggestion that the Pharmaceutical Manufacturers' Association (PMA) be invited to testify at the Committee's hearing. My view has been that because the PMA is legally prohibited from becoming involved in its members' price setting decisions, the Association can offer little specific factual information to the Committee. However, in the interest of providing invited firms every incentive to cooperate with the Committee's inquiry, Senator Heinz and I have sent PMA the enclosed letter of invitation. Please note that we do not view the Association's testimony as in any way replacing or lessening the need for manufacturers' participation in the hearing.

In addition, several firms' representatives have stated they are reluctant to participate because questions may be asked that would elicit confidential information. Please be advised that many of the questions Members may ask at the hearing will not be designed to elicit responses based on trade secrets or other confidential information. It is my hope and expectation that invited firms will decide to attend in order to assist the Committee by answering as many questions as possible.

I have instructed Committee staff to record each invited firm's final answer regarding requested data and testimony by no later than close of business June 30, 1989. Please consider the information in this letter and inform the Committee of your decision by that date.

Thank you for your consideration of the Committee's request.

Sincerely,

David Pryor

David Pryor
Chairman

Enclosure
DP:ds

[illegible]

United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

June 22, 1989

Mr. Gordon Binder
Chief Executive Officer
Amgen, Inc.
1900 Oak Terrace
Newberry Park, CA 91320

Dear Mr. Binder:

I am writing to advise you that the Special Committee on Aging hearing on prescription drug pricing, formerly scheduled for June 22, 1989, is now scheduled to take place at 9:30 a.m. on July 18, 1989, in room 628 of the Dirksen Senate Office Building. It is my sincere hope that the new date will prove convenient for you or a representative from your firm.

Please note that as of this writing, the Committee has received no written communication from your firm in response to my June 6, 1989 letter. I would very much appreciate receiving your written response to this revised invitation, together with the information and data requested, by 6 p.m. on June 30, 1989.

Thank you for your consideration of the Committee's request. If you have questions about this letter, please have your staff contact David Schulke or John Monahan at the Committee office at 202-224-5364 (telefax 202-224-9926).

Sincerely,

David Pryor
David Pryor
Chairman

DP:ds

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United States Senate
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WASHINGTON, DC 20510-6400

June 27, 1989

Mr. Winston Barton
Cabinet Secretary
State of Kansas
Department of Social and Rehabilitation Services
Docking State Office Building
Topeka, KS 66612-1570

Dear Mr. Barton:

I am writing to inform you that on Tuesday, July 18, 1989, the U.S. Senate Special Committee on Aging will convene a hearing on the subject of prescription drug manufacturer pricing policies and practices. This letter will confirm the Committee's interest in receiving oral and written testimony from you on the morning of the 18th, as discussed previously in conversations between Committee staff and Mr. Alquest, Commissioner of Income Maintenance and Medical Services.

This hearing will examine factors contributing to prescription drug cost increases in recent years, and explore opportunities in the current marketplace for third party payors, service providers and others to negotiate prescription drug purchase prices with manufacturers. Examples of negotiated prices of interest to the Committee include price discounts afforded by manufacturers to government agencies, such as your Medicaid program, the federal government's Departments of Veterans' Affairs and Defense, and to health care providers and buying groups, including hospitals, Health Maintenance Organizations, and retail pharmacies.

Committee Members would appreciate hearing your views on a number of issues related to prescription drug pricing, based upon your experience in managing the Kansas State Medical Assistance program's prescription drug procurements for many years. It will be most helpful if your testimony addresses the following questions:

1. What is the Kansas Medicaid Pharmaceutical Bidding Program? Why did your State undertake such a program?

2. In general, what is the magnitude of discounts realized by the Kansas Medicaid Pharmaceutical Bidding Program (both when expressed as a percentage of the published Average Wholesale Price at the time of purchase and as total estimated dollar savings) as a result of its negotiations with manufacturers for procurement of (a) multiple source and (b) single source prescription drugs?

3. What problems has the State encountered in attempting to negotiate prices with manufacturers? How successful has the State been in its efforts to resolve these problems?

4. What are the relative advantages of the Pharmaceutical Bidding Program as a means of containing prescription drug costs, compared to (a) reduced reimbursement to pharmacists, (b) limitations on the extent of coverage, such as a maximum number of prescriptions reimburseable per month or exclusion of new brand name products from coverage?

The Committee's hearing is scheduled to begin at 9:30 a.m. in room SD-628 of the Dirksen Senate Office Building. I would very much appreciate your providing the Committee with ten copies of your written testimony by close of business on July 13, and an additional 100 copies on the morning of July 17, 1989. Your testimony for submission into the record may be of whatever length you deem appropriate. The Committee would, however, appreciate your limiting oral remarks to no more than five minutes.

Thank you for your cooperation and assistance in this inquiry by the Committee. Should you have questions relating to this invitation, please have your staff contact David Schulke of the Special Committee on Aging office at 202-224-5364.

Sincerely,

David Pryor

David Pryor
Chairman

Enclosure
DP:dgs

Office of the Administrator
of Veterans Affairs
Washington, D.C. 20420

89 JUL -5 AM [illegible]

Rec'd by DGS 8/2/89

JUN 29 1989

Honorable David Pryor
Chairman, Special Committee
on Aging
United States Senate
Washington, D.C. 20510-6400

Dear Mr. Chairman:

Thank you for your letter of June 2, 1989, inviting Mr. Dennis M. Styrsky, Chief, Pharmaceutical Products Division, VA Marketing Center, to testify at a hearing before your Committee scheduled for July 13, 1989, regarding the subject of prescription drug manufacturer pricing policies and practices.

I am pleased to advise you that Mr. Styrsky will testify at the hearing; he will be accompanied by Charles E. Roberson, Director, Field Operations Service, Office of Acquisition and Materiel Management, Central Office.

The prepared statement will be provided in 150 copies, as requested.

Sincerely yours,

Edward J. Derwinski

Edward J. Derwinski
Secretary

"America is #1—Thanks to our Veterans"

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United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

June 30, 1989

The Honorable Louis Sullivan, M.D.
Secretary, Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

Dear Dr. Sullivan:

I am writing to inform you that on Tuesday, July 18, 1989, the U.S. Senate Special Committee on Aging will convene a hearing to examine the impact on prescription drug costs of manufacturer pricing policies and practices. This letter is to express the Committee's interest in receiving oral and written testimony on this subject from you or your designee on the morning of the 18th.

The Committee hearing will examine factors contributing to prescription drug cost increases in recent years, and explore opportunities in the current marketplace for third party payors, service providers and government to negotiate favorable prescription drug purchase prices with manufacturers. To facilitate your preparation, I would like to take this opportunity to specify the issues which your testimony before the Committee can most fruitfully address:

1. the findings of the Department's compilation of information, mandated by Section 1834(c)(8) of the Medicare Catastrophic Coverage Act of 1988, pertaining to manufacturers' prices, pharmacists' charges, and beneficiaries' use of covered outpatient drugs;

2. the results and process associated with the Department's recent discussions with Amgen, Inc., manufacturers of the prescription drug product "Epogen";

3. the Department's interest in being authorized to engage in negotiations and competitive bidding with single- and multiple-source prescription drug manufacturers, in order to achieve the lowest reasonable price for drugs purchased by or on behalf of Medicare and/or Medicaid beneficiaries.

I am very much looking forward to your testimony. In light of continuing uncertainty surrounding the financial stability of the Medicare prescription drug trust fund, I hope you too will see this hearing as a timely opportunity to explore policy options of great concern to older Americans.

The Committee's hearing is scheduled to begin at 9:30 a.m. in room SD-628 of the Dirksen Senate Office Building. Please instruct your staff to provide the Committee with ten copies of your written testimony by close of business on July 13. Copies of your testimony will be distributed in the Committee press packets if an additional 100 copies are delivered to the Committee office on the morning of July 17, 1989. Please note that your testimony for submission into the record may be of whatever length you deem appropriate. The Committee would, however, appreciate your limiting oral remarks to no more than ten minutes.

Thank you for your cooperation and assistance in the Committee's inquiry. Should you have questions relating to this invitation, please have your staff contact David Schulke of the Special Committee on Aging office at 224-5364.

Sincerely,

David Pryor

David Pryor
Chairman

[illegible]

United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

July 5, 1989

Mr. Bruce Laughrey, R.Ph.
President
Medi-Span Inc.
5980 West 71st Street
Indianapolis, IN 46268

Dear Mr. Laughrey:

I am writing to confirm that on Tuesday, July 18, 1989, the U.S. Senate Special Committee on Aging will convene a hearing on the subject of prescription drug manufacturer pricing policies and practices. On behalf of the Committee, I would like to invite you to present oral and written testimony on the morning of the 18th, as discussed previously in your telephone conversations with David Schulke of the Committee staff.

The Committee hearing will examine factors contributing to prescription drug cost increases in recent years, and explore opportunities in the current marketplace for third party payors, service providers and others to obtain favorable prescription drug purchase prices from manufacturers. The Committee would like to know the extent of price competition which may be associated with drug patent expiration, and whether competition has had the effect of moderating price increases in brand products once they lose patent protection.

I would like to take this opportunity to thank you for your willingness to employ Medi-Span's unique historical database to identify prescription drug price trends, and to specify the data of greatest utility to the Committee. If possible, your testimony should document and summarize in graphic form, based on the enclosed list of multiple source drugs most used by the elderly, trends in manufacturers' published brand and generic "Average Wholesale Prices" before and after patent expiration. To the extent feasible for each product on the enclosed list, please clearly identify in your graphic exhibits significant price changes associated with any of the following intervals in each chemical entity's marketplace "lifespan":

a. while the innovator product is being marketed under patent protection;

b. after the innovator product has lost patent protection, but before a generic competitor has secured marketing approval;

c. after the first generic competitor has begun to compete with the innovator product in the marketplace;

d. after the second and subsequent generic competitor products enter the market.

In summarizing your findings in testimony, it will be most helpful to the Committee if you will address these questions:

1. Is there a point in an innovator product's "lifespan" as it nears patent expiration when its manufacturer appears to reevaluate and significantly revise the product's pricing? If and when this takes place, in what way does the typical product's pricing change?

2. How often is the expiration of an innovator product's patent associated with either a decline or a slowed rate of increase in the innovator product's published "Average Wholesale Price"?

3. How often is the entry into the marketplace of one or more competing generic products associated with either a decline or a slowed rate of increase in the innovator product's published "Average Wholesale Price"?

4. Based upon this study of brand prescription drugs facing generic competition, what conclusions do you reach regarding the marketplace "price sensitivity" of manufacturers' published "Average Wholesale Prices"?

The Committee's hearing is scheduled to begin at 9:30 a.m. in room SD-628 of the Dirksen Senate Office Building. I would very much appreciate your providing the Committee with two copies of your graphic exhibits by July 12, to allow for enlargement and reproduction. In addition, please supply the Committee with ten copies of your written testimony by close of business July 14, and an additional 100 copies of testimony and exhibits on the morning of July 17, 1989. Please note that your testimony for submission into the record may be of whatever length you deem appropriate. The Committee would, however, appreciate your limiting oral remarks to no more than five minutes.

Thank you for your cooperation and assistance in this inquiry by the Committee. Should you have questions relating to this letter, please contact David Schulke of the Special Committee on Aging office at 202-224-5364.

Sincerely,

David Pryor

David Pryor
Chairman

Enclosure
DP:dgs

Multiple Source Drugs

Brand Name (Generic)	Strength	Dosage Form	Package Size
Tenormin (Atenolol)	50mg	tab	100
Dyazide (HCTZ & Triamterene)	50mg/25mg	cap	1000
Influenza Virus Vaccine type A, B.	----	inject.	5cc
Isordil (Isosorbide Dinitrate)	10mg	tab	100
Micro-K Extencaps (KCl)	10mg	SRcap	100
Lasix (Furosemide)	40mg	tab	1000
Inderal (Propranolol)	20mg	tab	100
Hydrodiuril (HCTZ)	50mg	tab	100
Motrin/Rufen (Ibuprofen)	800mg	tab	100
Deltasone (Prednisone)	5mg	tab	500
Aldomet (Methyldopa)	250mg	tab	100
Bactrim DS/Septra DS (Trimethoprim w/ sulfamethoxazole)	160mg/800mg	tab	100
Diabenese (Chlorpropamide)	250mg	tab	100
Theo-Dur (Theophylline)	300mg	SRtab	100
Keflex (Cephalexin)	500mg	cap	100
Antivert (Meclizine)	25mg	tab	100
Darvocet N (Propoxyphene Napsylate w/ Acetaminophen)	100mg/650mg	tab	500
Indocin (Indomethacin)	25mg	cap	100
Achromycin V (Tetracycline)	250mg	cap	100
Aldoril (HCTZ w/ methyldopa)	25mg/250mg	tab	100
Maxitrol (Dexamethasone, Neomycin, Polymixin)	0.1%	opth. susp.	5cc

Valium (Diazepam)	5mg	tab	500
Zyloprim (Allopurinol)	300mg	tab	100
Ativan (Lorazepam)	1mg	tab	100
Tolinase (Tolazamide)	250mg	tab	100
E-Mycin (Erythromycin)	333mg	ECtab	100
Polycillin (Ampicillin)	500mg	cap	500
Amoxil (Amoxicillin)	500mg	cap	100
Hygroton (Chlorthalidone)	50mg	tab	100
Elavil (Amitiptyline)	25mg	tab	100
Persantine (Dipyridamole)	50mg	tab	100

SINGLE SOURCE DRUGS

Brand Name (Generic)	Strength	Dosage Form	Package Size
Lanoxin (Digoxin)	0.25mg	tab	1000
Timoptic (Timolol)	0.5%	opth. sol.	10cc
Naprosyn (Naproxen)	375mg	tab	100
Lopressor (Metaprolol)	50mg	tab	100
Synthroid (Levothyroxine Sodium)	0.1mg	tab	100
Feldene (Piroxicam)	20mg	cap	100
Procardia (Nifedipine)	10mg	cap	300
Cardizem (Diltiazem)	60mg	tab	100
Transderm-Nitro (Nitroglycerin)	5mg	transdermal patch	30
Capoten (Captopril)	25mg	tab	100
Tagamet (Cimetidine)	300mg	tab	100
Zantac (Raniditine)	150mg	tab	60

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United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

July 11, 1989

Dr. John H. Gibbons
Director
Office of Technology Assessment
Washington, DC 20510-8025

Dear Dr. Gibbons:

I am writing to inform you that on Tuesday, July 18, 1989, the U.S. Senate Special Committee on Aging will convene a hearing to examine the impact on prescription drug costs of manufacturer price increases during the 1980s. This letter will confirm the Committee's interest in receiving written testimony on this subject from Dr. Judith Wagner on the morning of the 18th, as discussed previously on the telephone by Dr. Wagner and Committee staff.

Although I realize that the Office of Technology Assessment (OTA) has not conducted a study and has no report on this subject, I am very interested in having Dr. Wagner testify on matters covered in an excellent paper she prepared for the International Conference on Cost Containment in Three Countries, held in Bonn, Federal Republic of Germany in 1988.

The Committee's hearing is scheduled to begin at 9:30 a.m. in room SD-628 of the Dirksen Senate Office Building. I would appreciate your assistance in providing the Committee with 100 copies of Dr. Wagner's testimony on the morning of July 17, 1989. Please note that testimony for submission into the record may be of whatever length you and Dr. Wagner deem appropriate.

Thank you for your cooperation and assistance in the Committee's inquiry. So that you may be assured of an opportunity to observe the proceedings, I have instructed Committee staff to save a seat at the hearing for yourself and Dr. Wagner. Should you or Dr. Wagner have questions relating to this invitation, please have your staff contact David Schulke of the Special Committee on Aging office at 224-5364.

Sincerely,

David Pryor

David Pryor
Chairman

cc: Dr. Judith Wagner
DP:dgs

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Congress of the United States
OFFICE OF TECHNOLOGY ASSESSMENT
WASHINGTON, DC 20510-8025

JOHN H. GIBBONS
DIRECTOR

89 JUL 13 PM 6: 48

July 14, 1989

The Honorable David Pryor
Chairman
Special Committee on Aging
United States Senate
Washington, D.C. 20510-6400

Dear Mr. Chairman:

I am pleased to respond to your request for OTA to testify on trends in drug pricing and costs for the upcoming hearings on prescription drug costs and manufacturer price increases on July 18.

Dr. Judith Wagner will prepare the testimony and we will deliver 100 copies to the committee on the morning of July 17. If we can be of further assistance to you, please do not hesitate to call me or Dr. Wagner at 8-6590.

I appreciate your nice comments about Dr. Wagner's work.

With best wishes,

Sincerely,

Jack Gibbons

John H. Gibbons

WRITTEN TESTIMONY OF JUDITH WAGNER and BRIGITTE DUFFY
OFFICE OF TECHNOLOGY ASSESSMENT, U.S. CONGRESS
FOR THE SENATE SPECIAL COMMITTEE ON AGING

Drug Price Inflation and Cost Containment

July 18, 1989

In response to the Committe's request, we are submitting background information on recent trends in prescription drug spending and prices and a discussion of prospects for controlling expenditures for prescription drugs. The information that follows is based upon research we conducted in 1988 for an international conference on health care cost containment and not on any specific OTA project. A copy of that paper is appended to this testimony for the record. OTA has recently begun two studies related to the subject of this hearing. One will assess alternative methods for paying for prescription drugs under Medicare and the other will study trends in pharmaceutical R&D costs and returns. The testimony presented here is unrelated to either of these projects.

In 1987, $34 billion was spent in the United States for outpatient prescription and non-prescription drugs and medical supplies;[1] that is about 8 percent of this country's total spending for personal health care services. Seventy-three percent of that spending, or $25 billion, was for prescription drugs. Since 1980, national spending on drugs and sundries has increased at a slightly lower rate than personal health care expenditures as a whole (see chart 1). Between 1980 and 1987, spending on drugs and medical sundries rose by 81 percent, while personal health care spending rose by 101 percent. Since 1983, however, national spending for drugs and sundries rose at a rate very close to the increase in total personal health care spending--about 8.5 percent per year.

Despite the similarity in overall spending trends, the sources of the spending increases for drugs are very different from those for other components of health care. Virtually all of the increase in drug spending from 1980 to 1987 can be accounted for by increases in the prices that consumers must pay for these items.[2] Unlike other components of health spending, utilization factors such as increasing volume or a more expensive mix of drugs played a minuscule role in driving up drug spending. Chart 2 compares the sources of spending increases in drugs and sundries with those for total personal health care services and physician services. Forty-one percent of the increase in spending for physician services over the period is attributable to changes in utilization factors, whereas only 3 percent of spending on drugs and sundries is due to these factors. Price inflation is the key to drug spending increases in the 1980s.

What is behind the increase in drug prices? Chart 3 compares changes in prescription drug prices with the consumer price index for non-medical goods and services. Prescription drug prices rose much more rapidly than general price inflation in the 1980s. The purchasing power of a dollar for prescription drugs dropped by 48 percent between 1980 and 1987, compared to a 26 percent decline in the purchasing power of a dollar for non-medical items. We estimate that almost 60 percent of the increase in spending for drugs and sundries between 1980 and 1987 was due to increases in drug prices in excess of general price inflation.

To summarize the lessons from these trends, spending on drugs in the 1980s has generally tracked with overall inflation in health expenditures. With the Federal government about to take on new commitments for prescription drugs under the Medicare catastrophic health benefit, this component of health care expenditures will become increasingly important as a public policy issue. The data from the 1980s suggest that rising prices are the main drivers of increases in spending for prescription drugs; the success of efforts to contain expenditures for prescription drugs will depend in large measure on the ability to moderate the rate of prescription drug price inflation.

How can prescription drug prices be controlled? Two general approaches are available: making the market for prescription drugs more price competitive and imposition of direct payment limits by third-party payers. Generic substitution, and the price competition it encourages for drugs available from more than one company, is a powerful vehicle for moderating increases in drug prices. In 1980, almost 70 percent of all prescriptions were written for drugs available from multiple sources,[3] and the proportion is expected to increase further by 1990 when more drugs lose their market exclusivity.

The new Medicare Prescription Drug Benefit incorporates many features that stimulate price competition for multiple source drugs. For example, after the deductible has been reached, Medicare's payment level is set at the "median average wholesale price" unless the physician specifically writes on the prescription that "brand is medically necessary." This requirement for explicit physician override of generic substitution is, in our view, the strongest stimulus to generic substitution in the law. The law could have encouraged generic prescribing and dispensing even further by capping expenses that count toward the deductible at the median wholesale price of each multiple-source drug product. Doing so would have made Medicare recipients aware of the difference between the price they actually pay and the price at which the prescription could have been filled had they searched out low cost pharmacies and generic dispensing.

Despite the potential for more price competition with multiple-source drugs, the prices of the remaining 20 to 30 percent of prescriptions--those for drugs available from only one firm--are largely uncontrolled. The development of new "blockbuster" drugs in future years could raise prescription drug expenditures dramatically. There is little experience to draw on for successful models of cost control for these products. Most of the alternatives for controlling prices of these drugs, such as restrictive formularies or direct price setting, have both strengths and limitations. One promising approach may be to build into physicians' ordering practices, through changes in the organization and financing of health care, a sensitivity to the cost of one therapy versus another. Thus, the future course of prescription drug expenditures could be as closely tied to broad changes in the health care system as it is to specific strategies for drug price control.

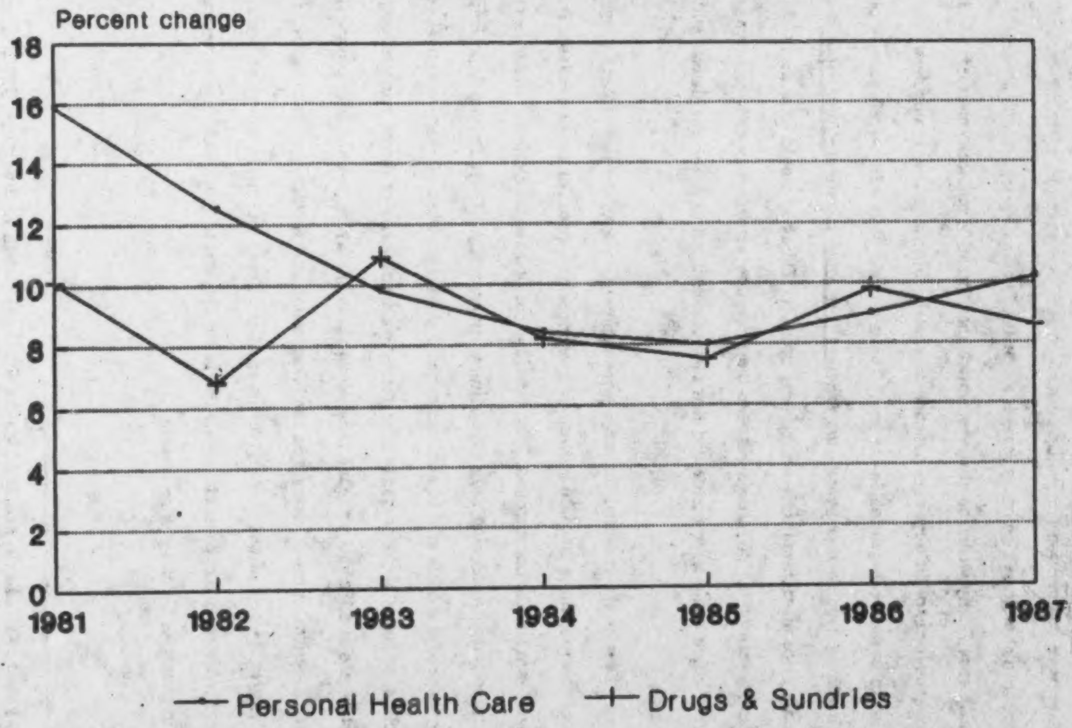
---

[1] S.W. Letsch, K.R. Levit, and D.R. Waldo, "National Health Expenditures, 1987," Health Care Financing Review 10(2):109-122, 1988.

[2] Consumer prices are measured by the consumer price index (CPI), which track drug prices at the retail level, not at the wholesale or manufacturing level.

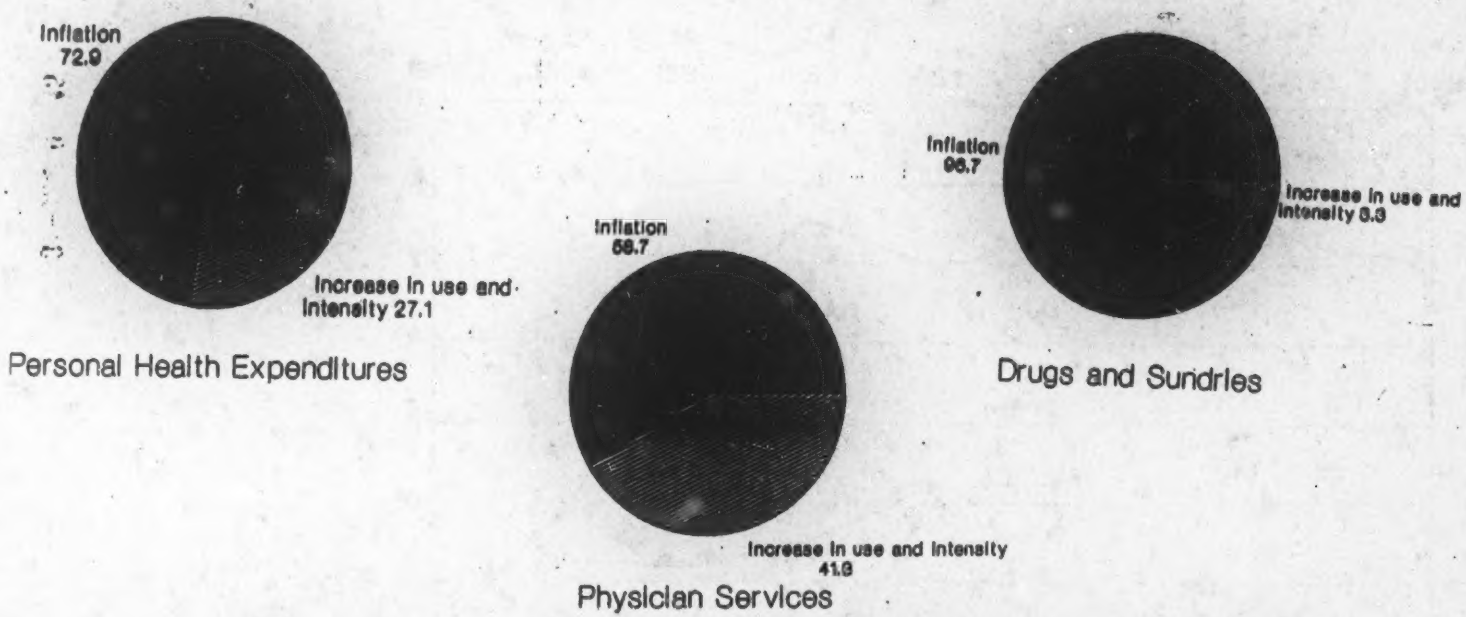
[3] A. Masson and R. Steiner, Generic Substitution and Prescription Drug Prices: Economic Effects of State Drug Product Selection Laws (Washington, DC: Federal Trade Commission, 1985).

Chart 1.--Annual Change in U.S. Personal Health Care Expenditures, 1981-1987 (in current dollars)



Source: OTA, 1989; calculated from data in "National Health Expenditures, 1987," Health Care Financing Review 10(2):109-121, 1988.

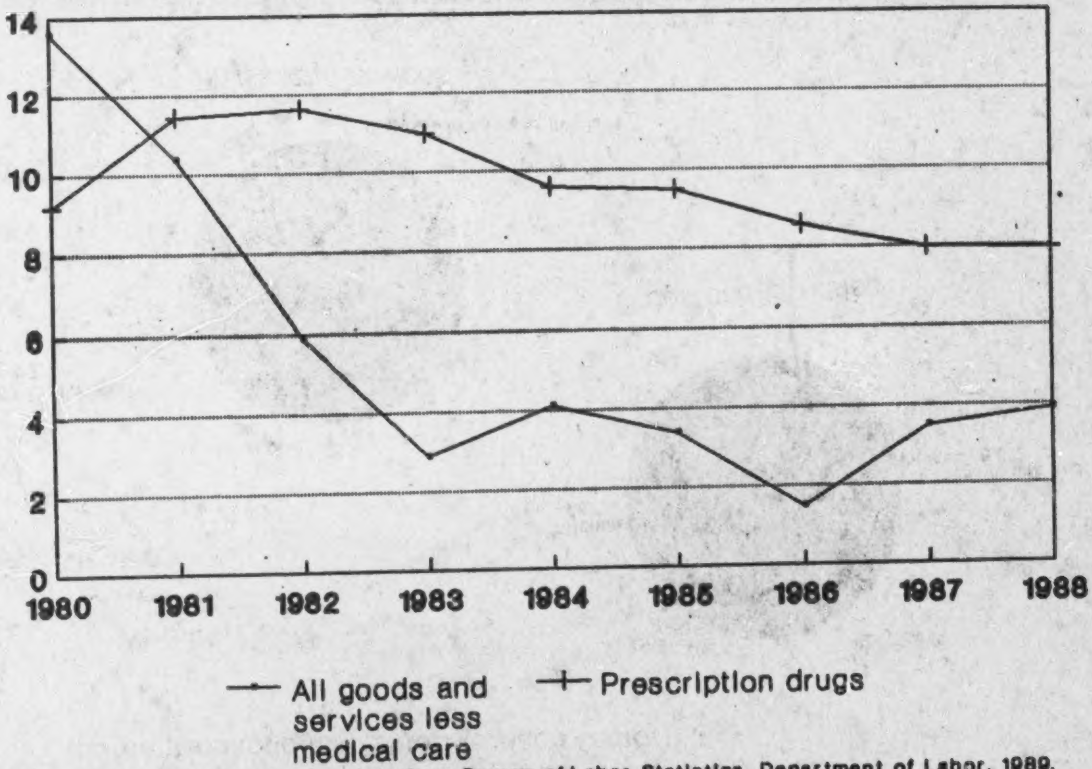
Chart 2.--Sources of Expenditure Change, 1980-1987*
(percent change attributed to each factor)



*Personal health expenditures are deflated by CPI-U for medical care; drugs and sundries are deflated by a weighted average of CPI-U for prescription drugs and CPI-U for non-prescription medical equipment and supplies; and physician services are deflated by CPI-U for physician services.

Source: OTA, 1989; calculated from data in "National Health Expenditures, 1987," Health Care Financing Review 10(2):109-121, 1988; and data from Bureau of Labor Statistics, Department of Labor, 1989.

Chart 3.--Percent Change in CPI-U for All Goods and Services (Less Medical Care) Versus Percent Change in CPI-U for Prescription Drugs



Source: OTA, 1989; calculated using data from Bureau of Labor Statistics, Department of Labor, 1989.

Containing the Costs of Prescription Drugs:
The U.S. Experience

Judith L. Wagner*
and
Brigitte M. Duffy**

for

International Symposium
"Controlling Costs While Maintaining Health"
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I
INTRODUCTION

This is an opportune time for a discussion of ways to contain the costs of prescription drugs in the United States and other countries. The U.S. government has just embarked on a major expansion of insurance coverage for prescription drugs for the 33 million Americans covered by the Federal Medicare program (the health insurance program for the elderly and disabled). The implementation of that new Medicare catastrophic prescription drug benefit may have a big impact on the ways that drugs are marketed, priced, prescribed and dispensed in the United States. Legislators and program administrators are understandably concerned about the effect the benefit will have on national expenditures and Medicare outlays for prescription drugs.

The future path of U.S. prescription drug expenditures may be already largely charted by the cost-control measures that have been adopted by State legislatures regarding prescription drug prescribing and dispensing practices, by Federal and State administrators of the Medicaid program (the health insurance program for the poor), and by the Drug Price Competition and Patent Term Restoration Act of 1984. The Medicare catastrophic drug coverage provisions will be implemented in the context of these other measures, enhancing some and counteracting the effects of others.

This paper describes and summarizes the evidence on the impact of the main approaches to cost containment aimed specifically at prescription drugs and examines how they are likely to act together in the future. More general cost-containment measures, such as adoption of prospective payment for hospitals or the development of health maintenance organizations (HMOs) and other at-risk health plans as an alternative to fee-for-service medicine, may in the long-run have important implications for prescription drug expenditures, but they are not discussed here.

The paper begins with a review of recent trends in spending for prescription drugs in the United States. These trends explain why cost-control efforts targeted specifically toward drugs have not been a main priority of health policy makers. Spending for prescription drugs has actually declined as a proportion of total health care spending since 1980. Whether that trend will continue, however, depends on a number of factors, including the quantity and therapeutic importance of future drug innovations and the speed with which cost-control measures are implemented in the future.

The second part of the paper focuses on cost control itself, describing the major cost control mechanisms adopted to date. The paper concludes with observations about how these approaches can be expected to change prescription drug expenditures in the future.

II
TRENDS IN PRESCRIPTION DRUG SPENDING

National Expenditures for Prescription Drugs: 1986

There is no single estimate of total U.S. spending on prescription drugs. The National Health Expenditures Series, maintained by the Office of the Actuary at the Health Care Financing Administration (HCFA), tracks the value of expenditures for "drugs and medical sundries." The estimate for 1986 is $30.6 billion, which is approximately 7.6 percent of total personal health care expenditures (HCFA, 1987).

This estimate is inaccurate for several reasons. First, the category includes over-the-counter (OTC) drugs and related items as well as prescription drugs. Second, it excludes all expenditures for patients who are hospitalized and some expenditures for patients in nursing homes.[1] In 1981, approximately 20 percent of drug purchases by pharmacies were made by non-Federal hospital pharmacies (IMS America, 1981). Third, it excludes purchases of drugs from retail establishments that are not primarily pharmacies and mail-order suppliers. Fourth, it excludes prescriptions dispensed directly by Health Maintenance Organizations (i.e., not filled at community pharmacies). In 1987, approximately 12 percent of all Americans were enrolled in HMOs (Interstudy, Inc., 1987), but the extent of direct dispensing by these organizations is unknown.

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[1] Expenditures for drugs dispensed by a hospital or nursing home and included in the institution's bill to the patient would be shown as a hospital or nursing home service.

HCFA is currently in the process of reestimating the National Health Expenditure Series back to 1960, and analysts predict that the largest adjustments will be in the "drugs and medical sundries" category (Waldo, 1988). After taking account of mail-order purchases and purchases in retail establishments that are not pharmacies (e.g., supermarkets with a pharmacy), HCFA actuaries expect 1986 spending in the category to be adjusted upward by roughly 10 percent (Waldo, 1988). After the adjustments are made, about two-thirds of these expenditures will be for prescription drugs; the rest will be for OTC drugs and related items (Waldo, 1988).

Taking into account all of these adjustments, we estimate that expenditures for prescription drugs in the U.S. in 1986 are approximately $26.7 billion, or about 6.5 percent of personal health care expenditures in the United States. This still modestly underestimates total drug expenditures, for it does not include expenditures by Federal hospitals[2] and unbilled expenditures for nursing homes and HMOs.[3]

Trends in Spending: 1980-1986

Chart 1 shows the trends in spending for drugs and sundries bought in pharmacies and for total personal health care services since 1980. Between 1980 and 1986 spending on drugs and medical sundries (as currently estimated by HCFA) increased by 66 percent in current dollars, compared to an 83 percent increase in personal health care spending. The percentage of personal health care expenditures accounted for by drugs and sundries dropped from 9 in 1980 to 7.8 percent in 1986. This decline is in part an artifact of the inadequate estimate of prescription drugs described above, since purchases outside of community-based pharmacies increased during the period and may account for as much as 10 percent of all drugs and sundries purchases today. Even if we were to assume that the entire extra 10 percent reflects new purchases since 1980, the total percentage increase in spending on drugs would be about 80 percent in the period, still a bit less than the overall increase in health care spending.

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[2] These consist mainly of the 172 Veterans Administration Hospitals.

[3] The total estimated value of manufacturer shipments (net of foreign trade) of pharmaceutical preparations for human use in 1986 was $24 billion (U.S. Department of Commerce, 1987). This estimate does not include biologicals such as vaccines or transportation and distribution costs, which should be included in the expenditure calculation. Nevertheless, this estimate is roughly in line with those from the National Health Expenditures series.

Of course, price inflation plays a major role in increasing expenditures for health care (Feder et al., 1987). Since 1980, the medical care component of the consumer price index (CPI) has been increasing much more rapidly than has the CPI for other goods and services, and prescription drug prices have increased faster than general medical care prices in that period. (See Table 1.) Chart 2 shows changes in spending for drugs and sundries after accounting for price changes.[4] In constant dollars, spending for drugs and sundries has remained virtually flat over the period. Roughly 50 percent of the increase in spending for drugs and sundries can be attributed to the general increase in the CPI; the remainder is largely due to the excess increase in drug prices over general price inflation. Only 3 percent is due to increases in the volume of drug purchases or in the complexity of the mix of drugs dispensed.

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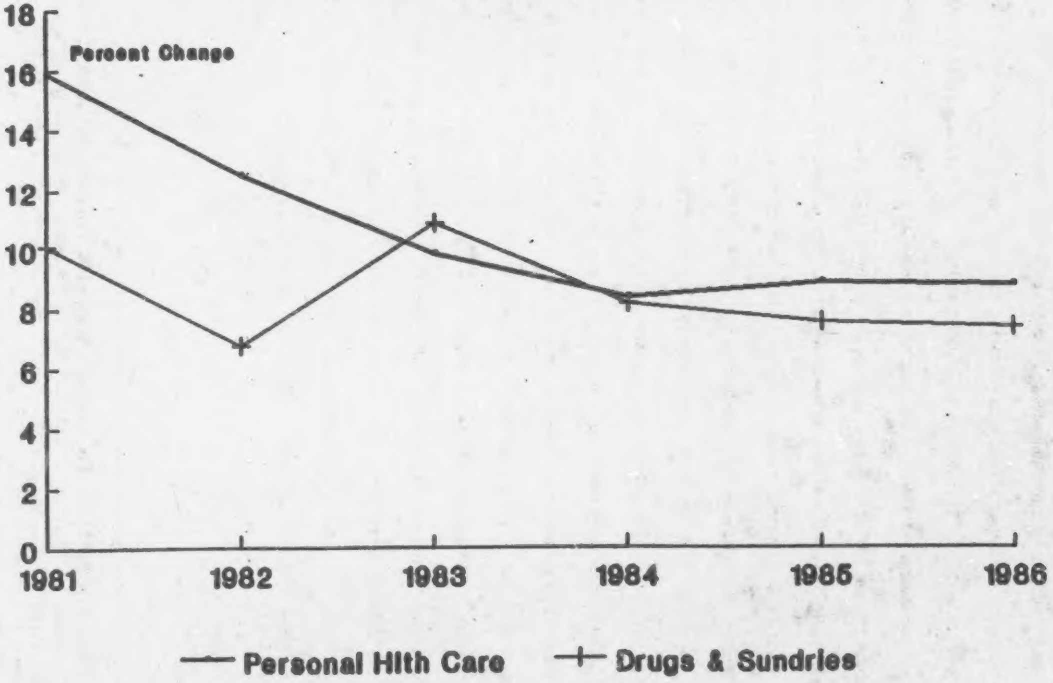
[4] The currently available HCFA estimates of spending for drugs and sundries was converted to constant dollars based on the assumption that 63 percent of drugs and sundries expenditures reported in HCFA's current National Health Expenditures Series were for prescription drugs; the rest were assumed to be for OTC drugs and medical sundries. This estimate of the prescription drug share is consistent with information on expected changes in the expenditure estimates provided by HCFA analysts (D. Waldo, 1988). The prescription drug share was deflated by the prescription drug component of the Consumer Price Index for urban areas (CPI-U); the other component was deflated by the non-medical component of the CPI-U.

Annual Change in U.S. Personal Health Care Expenditures

Current Dollars



Source: Health Care Financing Administration, 1987.

Table 1.--Price Inflation in the United States 1977-1987

Year	CPI-U all goods & services[1]	Percent change	CPI-U medical care	Percent change	CPI-U prescription drugs	Percent change
1976	57.2	NA	52.0	NA	53.9	NA
1977	60.8	6.29%	57.0	9.62%	57.2	6.12%
1978	65.4	7.57	61.8	8.42	61.6	7.69
1979	72.9	11.47	67.5	9.22	66.4	7.79
1980	82.8	13.58	74.9	10.96	72.5	9.19
1981	91.4	10.39	82.9	10.68	80.8	11.45
1982	96.8	5.91	92.5	11.58	90.2	11.63
1983	99.6	2.89	100.6	8.76	100.1	10.98
1984	103.7	4.12	106.8	6.16	109.7	9.59
1985	107.2	3.38	113.5	6.27	120.1	9.48
1986	108.8	1.49	122.0	7.49	130.4	8.58
1987	112.6	3.49	130.1	6.64	140.8	7.98

[1] This does not include the Medical Care component.

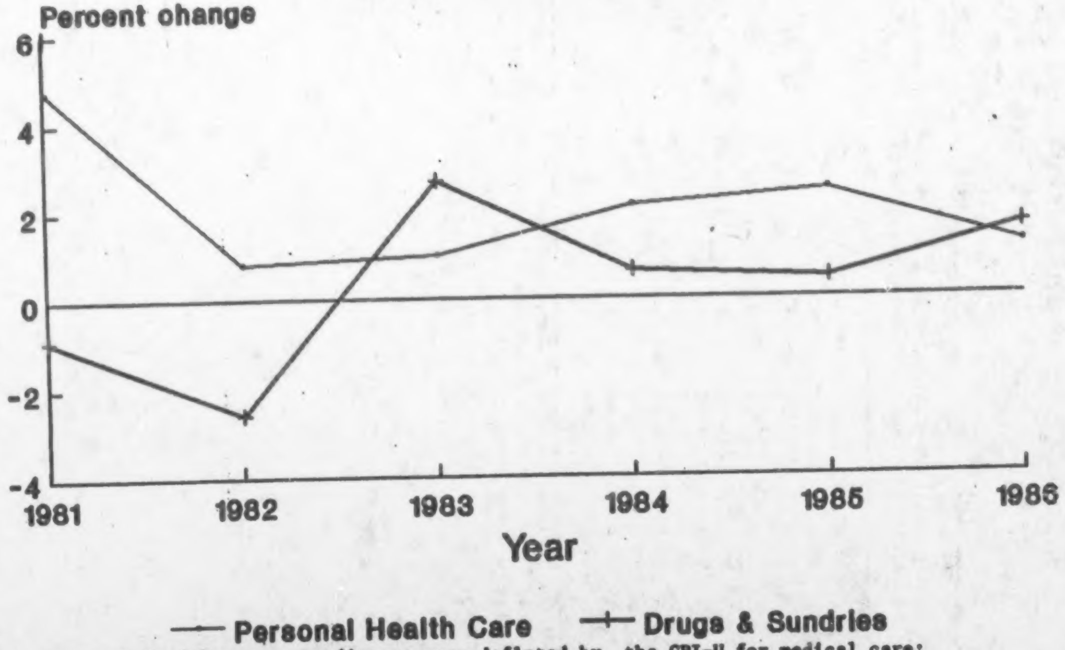
Abbreviations: CPI-U = Consumer Price Index - Urban; NA = Not applicable.

SOURCE: Bureau of Labor Statistics, U.S. Department of Labor, Washington DC, 1988.

Chart 2

Annual Change in U.S. Personal Health Care Expenditures

Constant Dollars 1982-1984



Note: Personal health care expenditures were deflated by the CPI-U for medical care; drugs and sundries expenditures were deflated by CPI-U for prescription drugs and CPI-U non-medical.

SOURCE: Health Care Financing Administration, U.S. Department of Health and Human Services, 1987; Bureau of Labor Statistics, U.S. Department of Labor, 1988.

In an analysis of drug expenditures for the Medicare population, Waldo estimated that the average cost of prescription drugs per enrollee increased 154 percent between 1977 and 1985, from $97 to $247 (Waldo, 1987). General consumer prices rose by approximately 176 percent during the period. The number of prescriptions per enrollee increased by only 16 percent over the eight years. Thus, if the elderly are any guide, over the longer period, since 1977, the major part of the increase in spending on drugs could be explained by general inflation.[5]

Sources of Funds for Drug Expenditures: 1986

According to data published for 1986, about 75 percent of all drugs and medical sundries are paid for directly by the consumer without the help of insurers or government subsidies (HCFA, 1987). Even taking into account expected changes in estimates of total expenses in this category, it appears that the consumer was directly responsible for about 73 percent of total expenditures for drugs and medical sundries and 60 percent of expenditures for prescription drugs. (See Table 2.) The share of third parties has grown steadily since 1980 as private insurance plans, HMOs, and State governments have added prescription drugs as benefits. The anticipated enactment of the Medicare Catastrophic Care Act of 1988 will, of course, further change the distribution of payment sources.

Implications for Cost Control

Despite the imprecision in the estimates of spending on prescription drugs in the United States, three conclusions are obvious:

- drugs and medical sundries account for a small proportion of total personal health care expenditures --between 6 and 7 percent; prescription drugs account for only about 4 percent of personal health care expenditures.
- spending for drugs and sundries is increasing more slowly than total spending for personal health care services;

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[5] Many clinicians would find a 16 percent increase over 8 years in the number of prescriptions per elderly Medicare beneficiary alarming for its potential implications for the quality of patient care. The point here is that, from the standpoint of health expenditures, a 2 percent per year increase in prescription drug use in the absense of price increases would look quite small compared to increases in other categories.

Table 2.--Source of Funds for Expenditures on Drugs and Sundries
United States, 1986

Source	Total drugs and sundries	Prescription drugs	Other items
All sources	100.0%	100.0%	100.0%
Direct consumer	73.5%	60.2%	100.0%
Private insurance	15.5%	23.3%	0.0
Government	11.0%	16.5%	0.0

SOURCE: Calculated from HCFA, 1987 data, adjusting for anticipated changes in spending estimates. These estimates assume that prescription drug expenditures were underestimated by 10 percent, that prescription drugs comprised 2/3 of total expenditures for drugs and sundries, that third-party payers and governments would not pay for any part of the non-prescription component, and that the additional 10 percent increase in estimated expenditures would be distributed among payers in the same way that current prescription expenditures are.

- o on the whole, since 1980, the use of drugs and sundries has not not increased substantially, at least not enough to raise alarms about its contribution to health care expenditures inflation.
- o Third-party payers, particularly Federal and State governments, cover less than half of all expenditures on prescription drugs.

It is not surprising, then, that cost control for prescription drugs has been a lower priority in the U.S. than has control of expenditures in other segments of the health care system. However, focussing only on general trends can mask serious problems of cost control, and policy makers have been actively addressing the problem of rising drug prices. The chief question has been whether prescription prices are rising for reasons that reflect changes in the costs of research and development (R&D), production and distribution, or whether the increases in drug prices are a reflection of monopoly power in the pharmaceutical industry (U.S. Congress, House of Representatives, 1987; Comanor, 1986). Because the consumer must pay for a large portion of prescription drug costs out-of-pocket, third party payers have taken only limited steps to control expenditures. Nevertheless, with the increasing coverage of prescription drugs by third-party payers, other approaches to cost control are now gaining widespread interest.

III

STRATEGIES FOR CONTROLLING THE COSTS OF PRESCRIPTION DRUGS

Cost control strategies for prescription drugs fall into two distinct but interdependent categories. One category comprises policies intended to make the market for drugs more price competitive. These general market competition policies arose from assessments of barriers to price competition in wholesale and retail drug markets. They represent efforts to eliminate or reduce barriers that insufficiently contribute to conflicting national objectives such as consumer protection and product innovation.

The second kind of cost control consists of strategies undertaken by public and private third party payers as part of their more general attempts to control program expenditures. Third party payer cost-control strategies fall into four sub-categories:

- raising beneficiary cost-sharing (e.g., increased deductibles, copayments);
- controlling the price paid by the third-party payer for a service or item;
- directly controlling the utilization of services or products; and
- bundling or packaging groups of services together for payment purposes.

The two kinds of cost control -- general enhancement of price competition and third-party payer strategies -- are interdependent, because actions taken in one area can alter the effectiveness of strategies in another. The ultimate in beneficiary cost sharing, for example, is the exclusion of prescription drugs as a benefit altogether. Such a policy would make consumers more price sensitive and would probably increase the potential effectiveness of strategies designed to reduce consumers' cost of search for retail price information. (It also puts the burden of expenditure for prescription drugs wholly on the patient.) For purposes of discussion, we will describe the approach to each kind of cost-containment strategy separately, emphasizing the important linkages among the approaches as appropriate.

Strategies Designed to Enhance Price Competition in the U.S. Market for Prescription Drugs

Federal and State efforts to enhance price competition in the wholesale and retail drug markets evolved from the realization that prescription drug prices were higher than they needed to be to assure both an adequate level of public safety and an adequate level of product innovation in the pharmaceutical industry. These artificially high prices were thought to arise from barriers to price competition, some of which are inherent in the structure of the industry and others which ensue from Federal and State health and safety regulations. Reform of such regulations has been the cornerstone of policies geared toward making the prescription drug market more price competitive. Recently, doubts have been raised about whether the reforms to date have been sufficiently effective in stimulating price competition (U.S. Congress, April 21, 1987) and whether the benefits of the price competition that does exist are passed on to the consumer by the pharmacist (Bloom et al., 1988).

Several features of the prescription drug market potentially give firms power to charge higher prices than would be sustainable in a competitive market.[6] First, patent protection, though available to all industries, is extremely important to the pharmaceutical industry (Comanor, 1986). Patent protection is a policy intended to stimulate innocation by conferring monopoly power to the developer of a new product or process for a limited time. During the period of protection for a specific drug product, the patent holder may choose to be the single source of supply for that product. Patent protection is limited to the specific product and therefore does not fully protect the firm from price competition with other drug products with similar therapeutic effects (Dao, 1984), but in general, the greater the real or perceived therapeutic benefits of a new drug over preexisting alternatives, the more effective is the patent in protecting the firm's market power.

Second, the introduction of new drug products is subject to rigorous regulation by the Food and Drug Administration (FDA), which requires extensive animal and human testing before a new chemical entity is approved for marketing. These requirements substantially add to the costs of development and delay the introduction of new drugs. The ultimate impact of FDA regulation of new drug development on the rate and quality of innovation has been the subject of vigorous debate (Comanor, 1986), but it is safe to say that when the potential market for a new drug is not large enough to justify the costs of meeting regulatory requirements, its introduction will be inhibited. Until 1984, FDA subjected all applications for marketing to the same evidentiary standards regardless of whether they were for a new chemical entity or for a new maker of a drug product whose patent has expired. Because manufacturers of "generic equivalents" of brand-name drugs that had lost patent protection had to invest substantial resources in clinical testing with the promise of capturing a small share of the market, many opportunities were foregone for increased price competition after patent expiration.

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[6] For a review of the literature on the economics of the pharmaceutical industry, see Comanor, 1986.

Third, and perhaps most important, virtually all prescriptions are written by physicians on behalf of consumers who are in large measure ignorant of generic or therapeutic alternatives. The prescription is an order for a specific drug entity, either by its chemical name (i.e., generic) or brand name. When a drug entity is manufactured by only one firm, the distinction between generic or brand-name prescribing is trivial; but when a specific drug entity is available from multiple sources, the physician has the therapeutic prerogative to insist that a specific brand be dispensed. Even when the physician holds no strong therapeutic rationale for prescribing the brand name, he or she may still write a prescription using the brand name out of habit or brand loyalty (Statman, 1981; Bond and Lean, 1977). In 1980, 79 percent of all prescriptions written for multi-source drugs in the United States were written for a brand (Masson and Steiner, 1985).

Procedures governing prescription dispensing determine how prescriptions for multi-source drugs are filled. State laws and traditional pharmacist practices have influenced these dispensing conventions. Because generic drugs are generally less expensive than their brand-name equivalents, policies to increase the frequency with which generics are either specified on the prescription or are substituted for brand-name prescriptions by the pharmacist offer the potential for saving hundreds of millions of dollars per year in expenditures for prescription drugs (Federal Trade Commission, 1979).

The two major initiatives intended to increase drug price competition have both focused on encouraging the use of generic equivalents for drugs whose patent protection has expired. The first initiatives were implemented at the State level throughout the 1970s, with the enactment of State laws repealing restrictions on the freedom of the pharmacist to substitute generic equivalents for brand-name prescriptions. The second was a 1984 Federal law, the Drug Price

Competition and Patent Term Restoration Act (Public Law 98-417), which permitted FDA to expedite the approval process for generic versions of brand-name drugs already found to be safe and effective by the FDA. Each is discussed below.

State-Level Generic Substitution Laws - Before 1970, most States had laws restricting the pharmacist's ability to substitute a lower-cost generic drug for a brand-name drug when the brand name was specified on the prescription form. By 1980, all 50 States had enacted drug product selection laws either requiring or permitting pharmacists to substitute generic drugs for the prescribed brand name drug as long as it was not expressly prohibited by the ordering physician. Despite the full diffusion of these laws throughout the States, generic substitution achieved only a toe-hold in dispensing practices. By 1984, only about 4 to 5 percent of all prescriptions written for a brand were subject to generic substitution (Masson and Steiner, 1985; Carroll et al., 1987). Masson and Steiner (1985) estimated that by 1984 consumer expenditures were reduced by about $130 to $240 million as a result of generic substitution.

The specific attributes of generic substitution laws have varied, however, and two recent studies have shown that some of these features have a major effect on substitution rates (Masson and Steiner, 1985; Carroll et al., 1987). Table 3 summarizes the findings of the two studies with respect to particular features of State law. Both studies support the conclusion that generic substitution laws are more effective when all three participants in the transaction -- the patient, the physician and the pharmacist -- are given incentives and information that encourages substitution. Patients appear to encourage substitution when they are informed of the alternatives, as the positive effects of the age of the law and requirements for patient consent demonstrate. Substitution is impeded if the pharmacist is required to pass on all savings from substitution to the consumer. Finally, the format of the prescription pad, and the inconvenience the physician is put through in order to insist on brand name dispensing, was found in both studies to be a strong predictor of the extent of generic substitution.

Table 3.-- Results of Studies of State Generic Substitution Laws

Variable	Study (direction of effect on rates of substitution)
Age of law:	
Number of years the drug product selection law was in effect	1(+)
Patient consent:	
Pharmacist must receive patients' consent to substitute a generic drug	1(+)
Additional record keeping:	
If substituting generics, pharmacist must keep additional records	1(-)
Savings transfer:	
pharmacist is required to pass savings on to the consumer	1(-), 2(0)
Prescription format:	
Two-line prescription pads (requiring positive action on physician's part to specify a generic)	1(-)
Degree to which pad makes it easy or difficult to substitute:	
-RXPRO (easy)	2(0)
-RXANTI (difficult)	2(-)
Formulary limitations:	
Lists of drugs that either may (positive formulary) or may not (negative formulary) be substituted for	1(-)
-negative formulary	2(0)
-positive formulary	2(-)
Liability protection:	
Pharmacist is protected from liability in substituting generics	1(+), 2(0)
Mandatory substitution:	
Pharmacist must substitute lower-priced drug as long as the prescriber has not prohibited substitution	1(+), 2(0)
Pharmacist hassle factor:	
Index of the extent to which the pharmacist must inform other parties involved, obtain consent of the consumer, and keep detailed records	2(+)

Key:

1 - N.V. Carroll, J.E. Fincham, and F.M. Cox, "The Effects of Differences in State Drug Product Selection Laws on Pharmacists' Substitution Behavior," Medical Care 25(11):1069-1077, 1987.

2 - A. Masson, and R. Steiner, Generic Substitution and Prescription Drug Prices: Economic Effects of State Drug Product Selection Laws (Washington, DC: Federal Trade Commission) 1985.

The Drug Price Competition and Patent Term Restoration Act - This law dealt simultaneously with two problems inherent in FDA new drug regulation. One problem stemmed from the erosion of effective patent terms due to the delay in new drug approval after a firm had received a patent. Brand-name producers argued that the delay effectively reduced their returns from innovation in new drugs and therefore reduced research and development outlays and rates of innovation (U.S. Congress, 1983). On the other hand, the costly requirements for clinical testing for market approval of any new drug, including generic equivalents, appeared to impede the introduction of generics to the market and to give the brand-name producers continued market power even after patent terms had expired.

The 1984 law struck a compromise between the two problems by extending patent terms to cover the period of drug lag while substantially reducing the testing requirements for approval of new generic drugs. Thus, while giving away more market power on the one hand, the law took away market power on the other.

By the end of 1986, FDA had approved over 1,000 new generic drug products under the provisions of the new law, and generic prescribing has increased rapidly since that time, although the trends are influenced by other factors in addition to the 1984 law (Nightingale and Morrison, 1987). These early gains in competition will be paid for later as new patented drugs are approved for marketing with longer patent lives. It is unclear whether the gains are worth the costs, because the costs of the law will depend on the rate of new drug development in the coming years, the therapeutic importance of the new drugs, and the speed with which competing therapeutic alternatives are developed to limit effective patent protection.

Effects of Competition-based Cost Control - The purpose of both initiatives described above was to introduce more price competition in the market for prescription drugs. The increasing share that generic drugs have of the total prescription drug market suggests that such competition is working. However, recent evidence collected by the U.S. House of Representatives Subcommittee on Health and the Environment suggests that, contrary to expectations, the

TABLE 4

PRICE CHANGES FOR SELECTED TOP-SELLING PRESCRIPTION DRUGS: BRAND NAMES VERSUS GENERICS

Brand Name	Date	Price change (%)	Generic Equivalent	Date	Price change (%)
Aldomet 250mg tab	1-1-85		Methyldopa 250mg	4/85-2/87	-27
	1-1-86	+10			
	1-1-87	+11			
Aldoril -25 tab	1-1-85		Methyldopa/HCTZ 25mg	2/86-2/87	-19
	1-1-86	+11			
	1-1-87	+11			
Ativan 1mg tab	1-11-85		Lorazepam 1mg	12/85-12/86	-52
	6-14-85	+11			
	11-13-86	+13			
Catapres tab 0.1mg	1-28-85		Clonidine HCL 0.1mg	5/86-2/87	-82
	2-3-86	+8			
	2-9-87	+9			
Dalmane 30mg	3-4-85		Flurazepam 30mg	12/85-11/86	-28
	1-6-86	+9			
	10-22-86	+8			
Darvocet-N-100	6-3-85		Propoxyphene-N-100/APAP	8/5-11/86	-19
	6-19-86	+9			
Diabinese 250mg	5-1-84		Chlorpropamide 250mg	10/84-12/86	-55
	6-1-86	+5			

TABLE 4 con't)

Inderal 40mg	1-2-85		Propranolol 40mg	7/85-1/87	-78
	1-2-86	+6			
	10-1-86	+7			
Indocin 25mg	1-1-84		Indomethacin 25mg	4/84-11/86	-60
	1-1-85	+8			
	1-1-86	+11			
	1-1-87	+11			
Valium 5mg	3-4-85		Diazepam 5mg	8/85-2/87	-83
	1-6-86	+8			
	10-20-86	+8			

Source: REVCO D.S., INC.

* These price changes were recorded for drugs purchased from pharmaceutical manufacturers by REVCO during the periods listed.

Table Source: U.S, Congress, Subcommittee on Health and the Environment, House of Representatives, Staff Report on Recent Increases in Prescription Drug Prices, June, 1987 prices of the top-selling brand-name drug products with generic alternatives increased rapidly in the 1984-1987 period at the same time that the prices of the equivalent generic products were decreasing. (See Table 4.) The reasons for these anomalous results are unclear, but several explanations are possible.

The American Association of Retired Persons claims that drug companies are charging more because they "discovered they can" (Guildroy, 1987). This would imply, of course, that before brand-name drug prices began their sharp ascent in 1980, the companies were ignorant of and failed to act on their substantial market power, an unlikely scenario. Companies may have exercised pricing restraint for strategic reasons --to avoid calling public attention to their substantial market power. Since the pharmaceutical industry was among the most profitable, companies were not under pressure to maximize short run profits by raising prices. As the industry came to grips with increasing competition from generics and loss of market share, drug companies may have changed tactics to emphasize product competition in market segments that would remain insensitive to price differentials.

Second, pharmaceutical companies may have been more successful in maintaining physician brand loyalty than was anticipated by those who crafted the generic reforms. Some have claimed that the companies have waged a campaign to discredit the true therapeutic equivalence of generic drugs[7] (Guildroy, 1987; Hutton, 1987). Perhaps firms have learned that brand-name products are luxury goods whose perceived value to the consumer or physician is a positive function of price. High price differentials between brand name drugs and their generic equivalents may call attention to the potential differences in product quality that major pharmaceutical companies wish to emphasize.

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[7] The Food and Drug Administration has made efforts to reassure the medical community about the safety of generic prescribing by clarifying its procedures governing the introduction and production of generic products (Nightengale and Morrison, 1987).

Another possibility is that the increase in private insurance coverage of prescription drugs in recent years may have reduced the cross-price elasticity of demand, thus enabling brand name manufacturers to increase prices. That such a trend could account for all of the price increase is unlikely, however.

The drug companies claim that prices are increasing because costs, particularly research and development costs, are increasing (Watson, 1987), but this would not make sense for products facing vigorous price competition from generics if by raising prices firms stood to lose substantial market share.

The wholesale drug prices listed in Table 4 do not reflect the manufacturers' total market. The prices shown reflect wholesale prices to a large community-based chain of pharmacies. The market for prescription drugs may be increasingly segmented, allowing suppliers to charge more competitive prices to volume purchasers such as hospitals, HMOs, or mail-order suppliers while raising prices to the segment with the lowest price elasticity of demand. But this is simply conjecture; data on actual prices to various customers has not been compiled to date. If this is indeed the case, we must ask why the community pharmacy segment of the market would be so price inelastic when consumers purchasing in this setting probably pay for a high proportion of drug costs out-of-pocket. Only insufficient knowledge of the alternatives and inadequate incentives to the pharmacist to inform consumers about the options would explain how the market could become segmented in this way.

Third-Party Payer Drug Cost Containment Programs

Third-party payers (public and private health insurers consisting mainly of Medicare, Medicaid and employer-sponsored group health plans) have substantially increased prescription drug benefits in recent years. Medicaid, the Federally-aided State-administered health plan for the poor, includes drugs as an optional benefit. All but three of the 51 Medicaid jurisdictions have a prescription drug plan. At present, Medicare does not cover outpatient prescription drugs except for immunosuppressive drugs in the year after transplantation, but beginning in

1991, a general catastrophic prescription drug benefit will be put into place. Despite the lack of coverage by Medicare, almost three-quarters of all elderly people have private supplementary insurance ("Medigap") policies which sometimes include prescription drug benefits (Gordon, 1986; Rice and McCall, 1985). As of 1987, eight States provided financial assistance to approximately 1.3 million eligible low-income elderly people for the purchase of prescription drugs through State Pharmaceutical Assistance Programs (U.S. Congress, OTA, 1987). Moreover, at present about 3 percent of Medicare beneficiaries are enrolled in capitated health care plans under a Medicare risk-sharing agreement; and many of these plans include prescription drugs as a benefit.

Private health insurance coverage of prescription drugs has grown rapidly, from 12 percent of all outpatient prescription expenses in 1977 (U.S. Department of Health and Human Services, 1982) to an estimated 23 percent in 1986. (See Table 2 above.) This growth in benefits has been accompanied by an increasing interest in controlling program expenditures, but to date few programs have been developed that are targeted specifically at drugs.[8]

This section reviews the experience of public third-party payers with strategies aimed directly at controlling prescription drug use or expenditures. The experience of the State Medicaid programs provides the richest source of information, not only because Medicaid has offered a more generous drug benefit than other third-party payers, but also because the States provide a natural laboratory in which the effectiveness of alternative cost control strategies can be assessed. Many features of Medicare's new catastrophic drug benefit are based on that experience. The review will therefore begin with a discussion of cost control under the Medicaid drug reimbursement programs. Then, we describe the outpatient prescription drug provisions of the recently enacted Medicare Catastrophic Coverage Act of 1988 and review its principal cost-control features.

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[8] Most private-sector drug cost-containment programs have focused on efficient claims processing and mail-order drug dispensing. Recently, pharmacy organizations and private firms have marketed capitated drug benefits to group health plans (Petricelli, 1988). These at-risk drug benefit plans have an incentive to purchase and dispense drugs at the lowest possible price and to review and control utilization as much as possible. These specialty preferred-provider organizations are relatively new, with a small market to date, but their importance is growing.

Medicaid Drug Reimbursement Programs

Although prescription drugs are an optional benefit under Medicaid, 48 of the 51 Medicaid jurisdictions in the United States currently have such a program. The specific designs of the programs differ, reflecting different approaches to expenditure control. Table 5 summarizes the main cost-control provisions in place in 1987. Cost-control strategies used by State Medicaid programs have included the following:

- Requirements for copayments by enrollees - Twenty States require the enrollee to pay a part of the drug charge, but in half of the States with this provision the copayment is quite low. Federal law prohibits the States from requiring children or pregnant women to share in the cost of Medicaid services, including drugs.
- Restricted formularies - These are lists of drugs that are approved for payment by Medicaid. Claims for prescription drugs that are not on the formulary are denied payment by the State Medicaid program. About 20 states had restricted formularies in 1987.
- Maximum payment limits for all drugs dispensed - Virtually all States pay a fixed dispensing fee and an amount to cover the ingredient costs. The median dispensing fee in 1987 was $3.50. Payments for the cost of ingredients were typically limited to the average wholesale price of the drug, with a few programs having limits somewhat less than the average wholesale price (National Pharmaceutical Council, 1987).
- Special limits, called Maximum Allowable Costs (MAC), on payments for multi-source drugs with at least 3 suppliers - The Federal Medicaid program issued regulations for a universal MAC program in 1976, which by 1983 included price limits on 57 separate drug entities[9] (Gagnon and Grabowski, 1983), but many States went further than required by the regulations in limiting reimbursement for other drugs that had generic equivalents. MAC programs set ingredient price limits based on a review of wholesale prices of all competing manufacturers of a given generic drug. An important feature of the MAC programs is the requirement that the prescriber certify in his or

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[9] In some cases these include different dosages of the same drug.

Table 5.--Cost Containment Provisions of
48 Medicaid Drug Reimbursement Systems, 1987

Cost containment provision	Number of states	Comments
Copayment requirement	20	Median copayment: $0.50; Range: $0.50-$3.00
Restricted formulary	20	
State MAC program	32	Median number of drugs included: 155; Range: 9-623
Maximum payment limits on all drugs	48	Median dispensing fee: $3.50; Range: $2.60-$5.12

Abbreviation: MAC = maximum allowable charge.
SOURCE: National Pharmaceutical Council, September 1987.

her own handwriting that a specific brand is medically necessary in order for the MAC price not to apply. This "physician override" requirement provides a powerful impetus to generic dispensing for Medicaid patients. The Federal MAC regulations were revised in 1987 to allow the States greater flexibility in implementing MAC programs, but the States must document that their expenditures for the drugs covered by Federal regulations do not in the aggregate exceed 150 percent of the least costly generic equivalent that can be purchased by pharmacists in reasonable quantities (Federal Register, July 31, 1987).

- o Dispensing Restrictions - Some States have established restrictions on the amount of a drug that can be dispensed at one time or on the number of prescriptions that can be reimbursed in any month. Limits on prescription size are intended to prevent hoarding or inappropriate drug sharing by enrollees, whereas limits on the total number of prescriptions are intended to discourage indiscriminate prescribing by physicians and drug use by Medicaid recipients.

- o Pharmacy Capitation Programs - For 8 months in 1981, the State of Iowa experimented with a program which paid pharmacists prospectively for the expected drug expenditures based on the types of Medicaid eligibles who chose them as their providers (Yesalis, et al., 1984). Pharmacists stood to gain financially from active involvement in the drug utilization review aspects of their profession. The program was ended after 8 months, when it became evident that it was not having its intended effects (Yesalis et al., 1984).

- o Drug Utilization Review - Eleven States have adopted a sophisticated program for reviewing patient use of drugs for their medical appropriateness and therapeutic implications. Underlying the programs is the assumption that inappropriate prescribing is not only bad medicine, but it also has implications for the use of expensive health care services such as hospitals or physicians. A proprietary therapeutic drug-use review program called DURbase identifies patients whose patterns of prescription drug use place them at risk of drug-induced illness (Health Information Designs, Inc.). Patient profiles built from claims data (including medical services and filled prescriptions) are monitored by computer on a monthly basis using therapeutic criteria to flag high-risk cases. Physicians and pharmacists review flagged profiles, and if a problem is still unresolved, letters are sent to physicians alerting them to the potential for drug-induced illness in their patients (Groves, 1985).

Numerous studies have been conducted examining the effects of particular strategies on Medicaid drug expenditures. They all suffer from research design flaws, so conclusions must be tentative. The MAC program was evaluated in two government-sponsored studies (HCFA, 1980; U.S. General Accounting Office, 1980), both of which concluded that the MAC program produced major savings for the Medicaid program. However, Gagnon and Grabowski have criticized both studies (Gagnon and Grabowski, 1983). First, they may have been based on un-representative samples of States and drug products. Second, the studies tend to underestimate the administrative costs of the program. Third, and most important, the studies did not adequately address the extent to which program savings to Medicaid were achieved at the expense of higher costs to other payers. Despite these criticisms, the impact of the MAC program on Medicaid drug expenditures has probably increased over time, and particularly after 1984, as more and more generic drugs came onto the market.

The use of copayment requirements has consistently reduced drug program expenditures (Smith, et al., 1982; Nelson, 1984; Soumerai et al., 1987). However, none of the studies of copayment examined the impact on overall use of Medicaid services or total program expenditures. Since copayment discourages consumers from filling prescriptions, negative impacts on health outcomes may also ensue. Possible effects in that area have not been examined.

Findings on the impact of restrictive formularies on Medicaid drug program costs are equivocal, but in general this approach has not been found to yield substantial savings in drug program or total Medicaid costs (Hefner, 1979; Smith et al., 1982). These findings have also been criticized for inadequate research design (Rucker and Morse, 1981). Restrictive formularies do pose bureaucratic obstacles for the addition of new drugs and may delay the availability of new drugs to Medicaid recipients.

Limiting the quantity dispensed at any one time has been found to save program expenditures (Smith et al., 1982), but restricting the number of prescriptions dispensed per time period, though cost-reducing in terms of Medicaid drug expenditures, may increase overall program expenditures and compromise the health status of the group that most frequently uses multiple prescriptions -- the elderly and disabled (Soumerai, 1987).

Drug utilization review programs have not been adequately evaluated. An anecdotal report on the State of Florida's experience with the DURBase program suggests that it has been favorably received by physicians and has saved medical care associated with preventable drug-induced illness (Groves, 1985). Considering that almost 200 million Medicaid prescriptions are processed each year, the administrative costs of drug utilization review, even with automated data processing and review systems, must be carefully considered.

In summary, the experience from Medicaid is that program expenditures can be curtailed by prudent pricing policies and copayment, but each of these approaches has implications that have not been adequately studied. The cost-shifting potential of Medicaid price stringency has not been assessed; and the implications for quality of care of copayment provisions have not been adequately investigated.

Catastrophic Outpatient Drug Coverage under Medicare

The Medicare Catastrophic Coverage Act of 1988 (Public Law 100-360) contains a new benefit under which Medicare beneficiaries with high annual expenditures for prescription drugs will receive some financial relief. The Catastrophic Coverage law represents a major departure for the Medicare program, because for the first time premiums are partially linked to incomes. The catastrophic drug benefit will be fully financed from special premiums paid by the elderly. The drug coverage provisions are to be phased in over a four-year period, with changes in the drugs covered, the deductibles required before the beneficiary is eligible for coverage, and the coinsurance rate. Table 6 contains a summary of the major features of the catastrophic drug coverage provision.

The drug payment provisions of the bill are summarized in Table 7. The bill is similar to the payment structure under most Medicaid programs, except that the Medicare bill sets up a "participating pharmacy" program which offers incentives to pharmacists to substitute generic

Table 6.--DRUG COVERAGE PROVISIONS:
The Medicare Catastrophic Coverage Act of 1988

Year	Drug Classes Covered	Deductible[1][2]	Coinsurance	Other Restrictions
cy 1990	a) Home Intravenous IV Therapy	$550	a) 20%	
	b) Immunosuppressive drugs beyond first year post-transplantation		b) 50%	
cy 1991	All Prescription Drugs	$600	50%	--Medicare will pay its full share (100% minus coinsurance) of the cost of th drug up to the payment limit; (See Table 7 for calculation o payment limit)
cy 1992	Same as Above	$652	40%	
cy 1993, etc.	Same as Above	Index based on 16.8% of Medicare beneficiaries exceeding deductible limit	20%	--dispensed quantity may be no more than 30 days supply unless authorized by DHHS

Notes:

[1] Expenses counting toward deductible based on actual expenses, not limited to payment limit amounts;

[2] Deductible waived for home IV drug therapy initiated during hospital stay and for immunosuppressive drugs in first year afte transplantation.

Abbreviation: cy = calendar year.

drugs for brand-name drugs in exchange for a higher dispensing fee.[10] In addition, the Medicare bill requires only two manufacturers to offer a given drug product with generic equivalents for it to be considered a multiple source drug.

Table 8 summarizes the features of the bill that are intended to control program expenditures. Many of the cost-containment features in Medicaid that have been found to be most effective have been adopted by the Medicare program. Of particular importance is the adoption by Medicare of the Medicaid MAC provision requiring physicians to write that a brand is medically necessary for the drug to be considered a single source product.

The program is designed to be fiscally solvent, and the Secretary of Health and Human Services will have the authority to control outlays by varying the deductible or keeping the coinsurance rate at 40 percent. The Department will also be able to change the method of calculating payment limits. Since Medicare will pay its share of the cost only up to the drug payment limits, changing the method of calculating payment limits can increase effective coinsurance rates for beneficiaries, who might then have to pay the balance between the payment limit and the actual charge. Since only non-participating pharmacists will be able to bill for the balance, reducing payment levels may discourage pharmacy participation in the program.

No one knows, of course, how the Medicare drug provisions will affect the prices of drugs for Medicare beneficiaries and other consumers. It is possible that the payment limits will become payment floors instead of ceilings, thus giving windfall profits to pharmacists at the cost to both Medicare patients and the program. The fact that the vast majority (84 percent) of Medicare beneficiaries will not become eligible for any benefits under these provisions may protect against this outcome, but consumers may be inefficient at searching out low-cost retail drug outlets (Bloom et al., 1986).

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[10] A participating pharmacist must accept the price Medicare sets as a limit for all drugs dispensed to a beneficiary after the deductible has been met. Since the payment limit for multi-source drugs is to be calculated as the median price across all available sources, the pharmacist will have an incentive to dispense the less expensive generic version.

Table 7.—Payment Provisions: Medicare Catastrophic Coverage Act of 1988

	Single Source Drugs	Multiple-Source Drugs
Definition	Covered outpatient drug product with no therapeutically equivalent, pharmaceutically equivalent, or bioequivalent alternatives or drug with restrictive prescription (requires physician to state on prescription that "brand is medically necessary")	Covered outpatient drug for which there are 2 or more drug products sold during the year that are: (a) therapeutically equivalent AND (b) pharmaceutically equivalent and bioequivalent¹
1990-1991	PMT = AWP x # of Tablets + AA where AWP = average wholesale price (excluding discounts) determined from (a) biannual survey of pharmacies, wholesalers, or direct sellers or (b) published wholesale prices for very low volume drugs AA = administrative allowance: $4.50 for participating pharmacy² $2.50 for other pharmacy	PMT=Median AWP x # of Tablets + AA where AWP = average wholesale price (excluding discounts) determined from (a) published AWP or (b) biannual survey of wholesale prices AA same as for single source drugs
1992, etc.	PMT=Minimum of: AWP x # of Tablets + AA or 90th pctile area-wide actual charges where AA is indexed by GNP implicit price deflator	Same as for 1990-1991

Notes:

[1] This requirement shall not apply if FDA changes the current definition of therapeutic equivalence as pharmaceutically equivalent and bioequivalent.

[2] Participating Pharmacy defined as one that agrees: (a) to accept payment on assignment-related basis for all drugs dispensed to Medicare beneficiaries that have met drug deductible; (b) not to refuse to dispense drugs to any Medicare beneficiaries; (c) not to charge Medicare beneficiaries more than it charges the general public; (d) to keep patient records for all Medicare beneficiaries; (e) to submit information on all purchases of covered outpatient drugs; (f) to counsel and advise patients on appropriate use and availability of equivalent drugs; (g) to provide [illegible] information in surveys.

Abbreviations: AA = administrative allowance; AWP = average wholesale price; GNP = gross national product; PMT = payment.

IV
CONCLUSIONS

Cost control strategies aimed specifically at prescription drugs have yet to demonstrate a significant impact on drug prices, at least as measured by published wholesale prices, but the structure to effect real changes in prescribing and dispensing practices in favor of lower cost drugs may be largely in place. Generic substitution laws, MAC-like third-party payment programs, and requirements governing dispensing conventions have increased the rate of generic substitution, and the advent of Medicare catastrophic drug coverage will strengthen these incentives.

The Medicare Catastrophic Coverage Law could have gone even further to encourage generic prescribing and dispensing had expenses counting toward the deductible been capped at the median wholesale price of each multi-source drug product. Medicare recipients would have been made aware of the difference in the price they actually pay and the price at which the prescription might be obtained by actively searching out low cost pharmacies and generic dispensing.

The key to containment of prescription drug expenditures appears to rest with the physician. Physicians can be given positive incentives to prescribe generic drugs and to consider less expensive therapeutic alternatives to expensive drugs, but they can also be made to pay for their brand loyalty with inconvenient and time-consuming prescription format requirements. The "physician override" requirement of the Medicaid MAC regulations and the Medicare Catastrophic benefits, if vigorously enforced, will further encourage moderation of drug expenditures.[11]

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[11] Enforcement of this requirement is important not only in its own right, but as a spur to State legislatures to revise the prescription pad formats so as to be in conformance with Medicaid and Medicare regulations.

Table 8.--Drug Cost Control Provisions of the Medicare Catastrophic Coverage Act of 1988

Direct Controls:

- Puts limits on payment levels for all drugs
    - -average wholesale price for single source drugs
    - -median of average wholesale price for multiple-source drugs.
- Requires Department of Health and Human Services (DHHS) to establish program to identify patterns of unnecessary or inappropriate prescribing; may deny coverage for "medically unnecessary" services.
- Requires physician to specify that brand is "medically necessary" on prescription for drug to be considered "single source" product.
- Limits number of doses dispensed at one time to 30 days or less.
- Gives DHHS authority in 1993 and 1994 to impose outlay controls (such as increasing deductible amount, halting reduction in coinsurance rate) to keep system solvent, except that it CANNOT:
    1) establish restrictive formulary,
    2) change method for calculating expenses for deductible, or
    3) increase coinsurance rate from preexisting rate.

Indirect Controls:

- Establishes Prescription Drug Payment Review Commission (PDPRC) to recommend changes in the system.
- Establishes "Participating Pharmacies" which agree to:
    - -charge prices within Medicare payment limits for Medicare patients receiving catastrophic drug benefits, and
    - -advise beneficiaries on availability of therapeutic equivalents.
- Requires DHHS to develop an annual guide containing comparative average wholesale prices of at least 500 of the most commonly prescribed covered outpatient drugs; the guide must be sent to all Medicare physicians, hospitals, and senior citizen centers.
- Requires physicians to submit diagnostic information on all physician claims (to allow development of drug utilization review systems linking drug prescribing to diagnosis).
- Requires DHHS study of potential for mail-order pharmacies as cost-control approach.
- Requires DHHS study of methods of Drug Utilization Review.

Although generic substitution is an important vehicle for moderating drug costs, it is not entirely sufficient. In 1980, 31 percent of all prescriptions were written for drugs available only from a single source (Masson and Steiner, 1985). It has also been estimated that by 1990, less than 20 of the top 100 prescribed drugs in the United States will have patent protection (Nomura Research, 1988). The prices of these single-source drugs -- those with current patent protection -- are largely unregulated.[12] When these drugs are perceived as therapeutically important by physicians and patients, there may be very little price elasticity of demand. Expansions of drug benefits under private and public health insurance further reduce the price elasticity of demand for these products. New "blockbuster" drugs for prevalent diseases such as heart disease, hypertension, and AIDS could potentially raise the share of prescription drugs in health care expenditures.

How will we control these expenditures in the future? By building into physicians' practices a sensitivity to the cost of one therapy versus another, the demand for single-source drugs can in some instances be made more price elastic. This paper has not discussed the implications for prescription drug expenditures of general trends in health care cost-containment, namely the introduction of capitated health care systems and other forms of payment bundling. Today, almost 13 percent of all Americans are enrolled in health maintenance organizations, and most of these plans include drugs in their benefit plans. To the extent that prescription drugs are included in the payment bundle, providers have the financial incentive to prescribe in a fashion that will reduce the total costs of the bundle and to prescribe the least expensive drugs available. HMOs also use restrictive formularies, volume purchasing, and selective contracting with pharmacies to achieve savings in drug costs (Patricelli, 1988). Thus, the future course of prescription drug expenditures may be as closely tied to broad changes in the health care system as they are to the specific cost-containment strategies discussed in this paper.

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[12] Medicaid MAC and Medicare limit payment amounts to the average wholesale price as determined by various methods; these limits discourage high mark-ups at the retail level, but they do not generally affect the manufacturer's price.

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GERALD HELLER, CHAIRMAN OF THE BOARD
RONALD L. ZIEGLER, PRESIDENT

July 28, 1989

The Honorable David H. Pryor
Chairman
Senate Special Committee on Aging
Room G-31 Dirksen Senate Office Building
US Senate
Washington, D.C. 20510-6400

Dear Senator Pryor:

On behalf of the National Association of Chain Drug Stores (NACDS), I would like to thank you for holding your hearing on prescription drug prices. NACDS represents more than 170 chain drug corporations operating in excess of 21,000 retail drug stores. Last year, the chain drug industry filled 37% of all prescriptions in this country. Therefore, the issue of prescription drug pricing is of paramount concern to us.

Creation of the new drug benefit program as part of the Medicare Catastrophic Coverage Act will have a profound impact on the chain drug store industry. The Congressional Budget Office (CBO) estimates that over 721 million prescriptions annually will be processed on behalf of 33 million beneficiaries under the new drug benefit program.

In his comments before your Committee, Louis B. Hays, Acting Administrator of the Health Care Financing Administration (HCFA) told the Committee that Medicare will pay the average wholesale price (AWP) for drugs covered under MCCA. He went on to say that AWP is significantly higher than actual costs of drugs. He compared AWP to the manufacturer's "sticker price" on a new car implying that it is rarely the price paid for the car or prescription drugs. Later, during the question and answer session, Mr. Hays claimed that Medicare payments of AWP for prescription drugs would provide significant financial rewards for retail pharmacies from the implementation of the drug benefit program.

It is misleading to claim that under the MCCA drug reimbursement provisions that pharmacists will receive payments of AWP for prescription drugs. The MCCA statute states that pharmacies shall receive reimbursement for multi-source drugs at a level that is the lower of the actual charge for the drug, or AWP plus a $4.50 administrative fee, or beginning in 1992, 90% of the actual charge of the drug. As a result, payments under the new law will never be more than the pharmacy's actual charge or usual and customary prescription charge. This amount is a price set by competitive market forces. CBO's analysis of drug expenditures by the elderly shows that the retail pharmacy market is indeed competitive.

The level of reimbursement of drugs will also be affected by lags in AWP price updates. The MCCA statute calls for a biannual survey to determine the AWP price for multi-source drugs. Once the survey is completed, the surveyed AWP price of the drug is not implemented until another six months later. Therefore, price updates may be delayed as long as up to 18 months and will in no way represent current AWP prices.

The combined effect of the "lower of" clause and the delayed updating of AWP effectively limits reimbursement under the MCCA to approximately AWP minus 10 percent plus an administrative fee of $3.85 (based on 1987 constant dollars.) In addition, payment updates historically have not kept pace with inflation. In the last decade, we have seen this payment lag with physician fees, hospital payments, and Medicaid dispensing fees.

Thus, statements by Mr. Hays perpetuates a fundamental misunderstanding of the issue of prescription drug reimbursement under the MCCA and prescription drug reimbursement in general. This continued misinterpretation has also permeated HCFA's reimbursement practices in the Medicaid program. NACDS believes the MCCA statute clearly defines the parameters for prescription drug reimbursement, and Mr. Hays' remarks only serve to further confuse the issue of prescription drug reimbursement.

In addition, NACDS strongly opposes implementation of an actual acquisition cost (AAC) reimbursement policy by public and private third party payers. Such action would be totally unacceptable to the retail pharmacy industry and does not represent the operation of the retail pharmacy marketplace and reimbursement policy.

NACDS believes any proposal to implement actual acquisition cost must be linked to payment of an adequate professional fee separate and distinct from the fixed administrative allowance fee contained in the MCCA. Fixed fees do not equitably compensate pharmacies for the differences in inventory and carrying costs for high-cost prescription drugs.

An actual acquisition cost reimbursement policy would remove incentives for retail pharmacy to be a product buyer and for a manufacturer to price drugs competitively. Such a proposal would substantially increase the cost of drugs to private and public third party payers and would be economically and politically unfeasible.

Finally, the retail pharmacy industry is highly competitive. Therefore, in order to keep their customers, most pharmacies cannot raise their prices on drugs when the manufacturer increases its prices.

NACDS recognizes that the MCCA drug benefit program presents a major challenge to the retail drug industry. The volatility of prescription drug prices in recent years adds another critical dimension to the retail pharmacy industry as they struggle to remain competitive.

As we move toward implementation of the drug benefit program we ask you to take our comments on drug pricing into consideration.

NACDS looks forward to working with this Committee and others to ensure that the drug program is financially sound and that it serves Medicare beneficiaries well. We would appreciate this letter being made part of the official hearing record.

Sincerely,

Ron Ziegler

Ronald L. Ziegler
President

NDC

MARK L. BRAUNSTEIN
President and
Chief Operating Officer

August 3, 1989

The Honorable David Pryor
Chairman
Special Committee on Aging
U. S. Senate, Room SD-G31
Washington, DC 20510

Dear Mr. Chairman:

I am writing to commend you for having conducted the hearing on "Prescription Drug Prices: Are We Getting Our Money's Worth?" As a physician and as an advocate of rational prescribing, I share completely your concern over rising drug costs.

I was also pleased to learn that you will be introducing legislation to mandate a comprehensive electronic drug utilization review system for Medicare's forthcoming outpatient prescription drug benefit. Enclosed for your consideration is an information paper, "Medicare Drug Utilization Review: Quality Assurance and Economy," which addresses the very same issue. The paper provides an overview of how and why a comprehensive electronic DUR system will vastly improve quality of care and substantially reduce health care costs borne by Medicare, Medicaid, private insurers, and the beneficiaries themselves. Should you deem it appropriate, I would very much appreciate your appending the information paper to your July 18, 1989, hearing record.

More than 15 years of commercial experience has placed NDC on the "cutting edge" of research and development technology in comprehensive, quick-response computer database-driven health care systems and programs. NDC's long tested and proven DUR system, DATASTAT, is in use in thousands of hospitals, clinics and pharmacies across the nation.

It has been suggested, however, that a comprehensive DUR system would be impractical and too costly for Medicare. NDC's experience is to the contrary, with a properly designed and implemented system. My contention, Mr. Chairman, is that Medicare and this nation's elderly cannot afford not to have a comprehensive DUR system.

Thank you for your interest in this important matter.

Sincerely,

Mark Braunstein

MARK L. BRAUNSTEIN, M.D.

Enclosure

MEDICARE DRUG UTILIZATION REVIEW: QUALITY ASSURANCE AND ECONOMY

AN INFORMATION PAPER

By

Mark L. Braunstein, M.D.
President and Chief Operating Officer
National Data Corporation
Atlanta, Georgia
July 1989

NDC

Foreword

Both the Congress and the Administration are to be highly commended for enacting the Medicare Catastrophic Coverage Act of 1988. The Act includes an outpatient prescription drug benefit for the nation's 34 million Medicare beneficiaries, which will be phased in over a three-year period, beginning in January 1991.

Equally, if not more, important to Medicare coverage of outpatient drugs is a provision in the Act for quality assurance through a computerized drug utilization review (DUR) system. If designed and operated properly, this electronic DUR system will greatly improve quality of care and save the Medicare program and its beneficiaries billions of dollars each year. Medicare, Medicaid, private insurers, and the beneficiaries themselves will spend less on drugs, which cost $18.00 on average for each prescription. More importantly, prevention of inappropriate and excessive prescribing through electronic DUR can substantially reduce the number of serious and life-threatening adverse drug reactions and interactions. Untold thousands fall victim every year to these preventable adverse reactions, which all too often lead to costly hospitalization and sometimes even death.

National Data Corporation has developed, through advanced computer technology in health care systems, a highly sophisticated and proven electronic DUR system for ensuring safe, appropriate, and cost effective drug dispensing.

Mark L. Braunstein, M.D.

Medicare DUR: A Solution To The "Other Drug Problem"

Inappropriate and excessive prescribing for the elderly has come to be known as our nation's "other drug problem."

Government-sponsored and university-based studies show all too clearly that the elderly often are victims of unnecessary, and sometimes dangerous, drug prescriptions. Older adults are more likely to be taking multiple medications for multiple illnesses, requiring the specialized care of two or more physicians. Consequently, the elderly are more likely to experience adverse drug reactions and interactions; and, as sensitivity to many medications increases with age, adverse reactions suffered by the elderly often are more serious.

A 1986 Harvard Medical School Health Letter stated that "research shows over-medication and adverse reactions to drugs are prevalent and have probably become epidemic among the elderly."

While individuals 60 and older represent only 17 percent of the nation's population, half of the deaths and over a third of the hospitalizations caused by adverse drug reactions reported to the FDA occur in this older population.

The Public Citizen Health Research Group's (PCHRG) recently published study, "Worst Pills Best Pills," estimates that in 1985 "243,000 older American adults (60 and older) were hospitalized because of adverse reactions to drugs they were taking before their hospitalization." PCHRG further estimates that each year:

- "More than 9 million adverse drug reactions occur in older Americans;
- "32,000 older adults suffer from hip fractures attributable to drug-induced falling;
- "163,000 older Americans suffer from serious mental impairment [memory loss, dementia] either caused or worsened by drugs;
- "2 million older Americans are addicted or at risk of addiction to minor tranquilizers or sleeping pills because of using them daily for at least one year; and
- "73,000 older adults have developed drug-induced tardive dyskinesia [uncontrollable and involuntary movements and shaking], the most serious, common, and often irreversible adverse reaction to antipsychotic drugs."

A study conducted by Vanderbilt University researchers in 1986 revealed highly inappropriate and excessive prescribing of powerful and potentially dangerous antipsychotic drugs for elderly nursing home residents in Tennessee. Almost 40 percent of the 20,500 dually eligible Medicaid/Medicare nursing home residents between the ages of 65 and 84 were prescribed these incapacitating medications which are normally used for treating schizophrenia in younger individuals.

Harvard researchers reported in late 1988 on the use of psychoactive medications in a representative sample of intermediate care nursing homes in Massachusetts. They found that over half of the 850 residents in these nursing homes were taking a prescribed psychoactive drug, including antidepressants, sedative/hypnotics, and powerful antispychotics.

In 1988, a report by the Special Committee on Aging of the U.S. Senate stated that in 1986, "as many as 120 million prescriptions (for elders) costing more than $2 billion" may have been "inappropriate." The report emphasized the need for a computerized electronic DUR system to reduce prescribing of addictive and powerful tranquilizers and antipsychotic drugs for the elderly Medicare beneficiaries, especially those residing in nursing homes.

A recent study by the Inspector General, U.S. Department of Health and Human Services reports that "Nearly every prescription written in 1988 by physicians who graduated from medical school in 1960 is for drugs about which those physicians have received no formal education." The Inspector General also cited an earlier study conducted by researchers at Temple University Medical School, which showed that more than 70 percent of a group of physicians surveyed failed a test on knowledge of prescribing for the elderly.

The Need for Electronic DUR In Medicare

Pharmacists have long practiced drug utilization review as an integral part of quality assurance and prevention of drug-induced adverse reactions. DUR, however, has become increasingly important because of dramatic increase in the number of drug therapies over the last half century.

Physicians now have more than 10,000 prescription drugs from which to choose in treating their patients. Consequently, most physicians find it extremely difficult, if not impossible, to keep abreast of the latest information on the thousands of potential adverse drug reactions and interactions associated with this huge and growing assortment of drugs.

The role of the pharmacist, therefore, has taken on increasing importance in detecting potential adverse reactions. Fully cognizant of this responsibility, pharmacists for years have kept close at hand such comprehensive compendia as the U.S. Pharmacopoeia "Drug Information for The Health Care Provider" and the "Hospital Formulary." These voluminous reference compendia contain information on appropriate prescribing of medications, and precautions and warnings concerning potential adverse effects of certain drugs taken by themselves or in combination with other drugs.

Potentially severe drug interactions alone number in the thousands, not to mention allergic and cross-sensitivity reactions, harmful drug-to-illness/condition effects, and reactions to incorrect dosage. As the number of new drugs continued to grow, day by day, so did the amount of time spent by the pharmacist to insure safe and appropriate drug dispensing. Pharmacists needed a quick, efficient and accurate way of retrieving this information which is so crucial to their patients' welfare, especially the elderly. Computer technology provided the solution.

Electronic DUR Is Already In Use

Today, at least 70 percent of the nation's 65,000 independent and chain pharmacies rely on some form of computerized electronic DUR. The Department of Defense (DoD) began a decade ago to install National Data Corporation's electronic DUR systems in its vast network of military hospitals, clinics, and pharmacies.

While these pharmacists continue to keep on hand their voluminous drug information reference compendia, the electronic DUR can almost instantaneously place at their fingertips the same vital information on their patients' prescriptions.

The need for electronic DUR was recognized over a decade ago by forward-thinking pharmacists in both the private and government sectors. The worth and necessity of this time-tested mechanism was proven and established years ago. This nation's 34 million Medicare beneficiaries surely are deserving of no less.

Electronic DUR Has Wide Support

Electronic DUR for Medicare outpatients is supported by many professional and public interest groups, including: the American Medical Association (AMA); the American Pharmaceutical Association (APhA), representing the nation's pharmacists; the American Society of Hospital Pharmacists (ASHP); and the American Association of Retired Persons (AARP), a strong advocate of quality assurance and economy in Medicare. AARP represents 24 million members 50 years and older.

Moreover, the Drug Utilization Review Act of 1989 was introduced recently in both the U.S. Senate and House of Representatives to clarify and specify the intent of both bodies for a comprehensive Medicare DUR system. The Act also provides strict legal safeguards for protecting the privacy of Medicare beneficiaries and the confidentiality of patient-specific drug information. Senators Pete Wilson and John Heinz, original drafters of the bill, recognized that although less than 17 percent of Medicare beneficiaries will receive reimbursements because of Medicare deductibles, all beneficiaries will enjoy the benefit of drug utilization review. In addition to vastly improved quality assurance in drug utilization, the elderly will spend less on out-of-pocket drug costs.

NDC's Electronic DUR System, And How It Works

National Data Corporation launched its intensive ongoing effort to address the critical information needs of pharmacists 15 years ago, and continues to be in the forefront--on the "cutting edge"--of electronic DUR technology.

In addition to providing its systems to more than 200 DoD medical facilities, including Walter Reed and Bethesda Naval Medical Centers, NDC's electronic DUR is being used in thousands of pharmacies serving the general public, nursing home residents, and public and private health care institutions across the nation. The pharmacy in the U.S. Capitol, which serves the 535 members of the Senate and Congress, has relied on NDC's electronic DUR for the past eight years.

DATASTAT®: NDC's Electronic DUR System

DATASTAT® is especially effective in that it provides the pharmacist with essential information on potential problems before the drug is dispensed.

DATASTAT® is a comprehensive, quick-response system which records on computer all pertinent information on each of the drugs prescribed for an individual patient. DATASTAT® can, in a matter of a few seconds, alert the pharmacist of the following potential adverse effects:

- Severe to mild reactions due to interaction of two or more drugs being taken concurrently;

- Severe to mild reactions caused by two or more drugs from within the same therapeutic class;

- Potentially dangerous allergic reactions to drugs;

- Harmful effects caused by noncompliance in taking medications, and by drug overdosing and abuse; and

The newest DATASTAT® alerts recently completed by NDC include:

- Serious reactions caused by excessive drug dosage and duration;

- Drug-induced problems caused by an interaction between a drug and an existing disease state.

DATASTAT®'s utilization review for drug-to-drug interactions alone contains alerts for more than 8,000 potentially severe adverse reactions. In addition to identifying the "problem drugs," DATASTAT® displays on the computer terminal a description of the potential reaction or interaction. For purposes of consultation regarding a potential problem with the prescription(s), the pharmacist may also retrieve from DATASTAT® the identities of the prescribing physician(s) and other pharmacists who may be serving the patient.

DATASTAT® Addresses Causes Of Inappropriate Prescribing

DATASTAT® is sensitive and responsive to the needs of the prescribing physician and dispensing pharmacist, as well as to the Medicare beneficiary. DATASTAT® provides safeguards against the pitfalls of misinformation and the lack of information which may work against the conscientious efforts of dedicated physicians and pharmacists.

The report published by the Senate Special Committee on Aging in late 1988 correctly states that "The reasons [for inappropriate prescribing] can be attributed to the physician, the patient or both," and cited the following examples:

- "The patient may intentionally or unintentionally fail to inform one physician that he or she is receiving prescriptions from one or more other physicians;

- "The physician may fail to question the patient about whether he or she is receiving prescriptions from other physicians;

- "The physician may not obtain complete information on the patient's medical condition which could affect the patient's response to the drug prescribed;

- "The patient may fail to inform the physician of allergic reactions to certain medications;

- "The physician may neglect to question the patient about allergic reactions to medications;

- "The physician may prescribe the wrong dosage; and

- "The physician is fully aware of the patient's condition, allergies and all of the patient's prescriptions, but mistakenly orders an unnecessary or potentially harmful prescription."

The Senate report makes clear that, in addition to protecting the patient from adverse reactions, a comprehensive, quick-response DUR system also safeguards both the prescribing physician and dispensing pharmacist from the potentially disastrous consequences of misinformation as well as the lack of information.

HCFA's Requirements for Medicare's Electronic DUR

The Health Care Financing Administration (HCFA) is the federal agency charged with developing and implementing by January 1, 1991 Medicare's computerized electronic point-of-sale (POS) system which includes Medicare's electronic DUR system.

The POS will receive from the pharmacist via computer terminal all information on a prescription necessary for the Medicare claims processing and DUR functions. The claims processing portion of the electronic POS will process Medicare outpatient drug bills to determine if a beneficiary claimant is eligible and when the beneficiary meets and satisfies the deductible prior to Medicare reimbursement for outpatient prescription drugs.

The task of setting up such a nationwide system for processing 720 million or more drug prescriptions yearly is by no means an easy one. HCFA is deserving of high praise and commendation for what has already been accomplished in development and planning of the POS overall.

HCFA issued its request for proposal (RFP) on July 18, 1989, inviting private contractors to submit bids for developing, operating, and maintaining the POS according to HCFA specifications defined in the RFP.

HCFA officials have consulted over the past year with individuals and organizations in the government and private sectors and in academia. NDC presented its DATASTAT® electronic DUR system to HCFA several months ago; and, following HCFA's issuance of the draft RFP this past May, NDC submitted its comments to HCFA regarding draft RFP specifications. NDC very much appreciated having had the opportunity to present its thoughts and views to HCFA and the public regarding the claims processing and DUR functions of the POS.

As the nation's largest independent processor of point-of-sale (POS) transactions and a leading provider of electronic DUR to pharmacies, hospitals, nursing homes, and health care maintenance organizations (HMOs), NDC fully supports the concept of HCFA's program. But NDC reiterates its finding to HCFA in NDC's earlier comments on the draft RFP: "...HCFA's innovative DUR program... falls short in a number of critical, clinically significant areas."

NDC continues to recommend that HCFA broaden and strengthen its requirements and provisions for the electronic DUR system. As noted earlier in this report, DATASTAT®'s surveillance of drug-to-drug interactions alone contains more than 8,000 pairs of interacting drugs capable of causing potentially severe adverse reactions. HCFA's draft RFP lists only 231 such pairs; and, while this list of drug pairs does not appear in the final RFP, HCFA states that, at the time of contract award, it will provide an "initial list of 225 to 250 severe drug-drug interactions." An analysis of the draft RFP's list of 231 interacting drug pairs shows that NDC's DATASTAT® contains an additional 930 (75 percent more) severe interacting combinations associated with the draft RFP's list of 231.

The American Pharmaceutical Association (APhA), American Society of Hospital Pharmacists (ASHP), and the American Association of Retired Persons (AARP) have recommended to HCFA in their comments on the draft RFP that the DUR component of the POS be expanded to include more interactions. AARP stated that it "believes that the DUR specifications as described in the draft RFP fall far short of Congress' mark." Regarding the draft RFP's DUR coverage for detecting problems with therapeutic duplicates, severe potential drug interactions, and adverse effects from excessive dosage, the ASHP stated, ". . .ASHP is extremely concerned about the incomplete and inaccurate information included in these three items" (emphasis not added).

More recently, the U.S. General Accounting Office (GAO) issued a report, "HCFA's Proposed Drug Utilization Review System Ignores Quality of Care Issues," requested by the U.S. Senate Special Committee on Aging. The GAO report, issued less than a week after issuance of HCFA's RFP, states in part:

> [D]rug utilization review systems exist with capabilities far beyond those of the system being proposed by HCFA. . . [T]he minimal DUR system proposed by HCFA is unlikely to be able to provide adequate information on safety. . . [I]t is unclear why HCFA is developing its own DUR system when more comprehensive and well-tested systems already exist... HCFA's emphasis has been on financial considerations (specifically, bill paying procedures) rather than on the health and safety aspects of [DUR]... [B]oth the Congress and HCFA's top managers should understand the severe limitations of the system's capabilities.

Analysis of the "top 25" prescription drugs used by the elderly in 1986[1] reveals large gaps in the list of 231 drug interactions provided in the draft RFP for screening in the Medicare DUR. HCFA, however, did not include in its final RFP a list of the 225 to 250 which the agency plans to provide at the time of contract award. Therefore, it is not known at this time whether there will be changes in the drugs chosen for screening. Nonetheless, HCFA's anticipated list of 225 to 250 interacting drugs for DUR screening will represent less than half of the potentially severe adverse interactions for the "top 25" drugs contained in NDC's DATASTAT®.

Should HCFA provide to its contractors at the time of award the same list of 231 interacting drug pairs contained in the draft RFP, this very limited list will fail to consider and address potentially severe adverse interactions involving 13 of the

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[1] "Drug Utilization in the U.S.-1986, Eighth Annual Review," Dec. 1987, by the Food and Drug Administration's (FDA) Office of Epidemiology and Biostatistics, p.18. Table 7, which contains the heading "Prescribing of Drugs in 1986 for the Elderly (65 and Older)," lists the "top 25 Drugs as Specified by the Prescribing Physician." The list includes: Lasix; Lanoxin; Dyazide; digoxin; hydrochlorothiazide; Inderal; aspirin; Persantine; Theo-dur; nitroglycerin; insulin NPH; Coumadin; prednisone; Aldomet; Procardia; Isordil; Motrin; Tylenol with codeine; Tagamet; Cardizem; Capoten; Tenormin; Lopressor; Timoptic; and Zantac. This table presents the latest such data published by the FDA. It is generally assumed that most of these medications have remained among those drugs heavily prescribed for the elderly since 1986.

"top 25." NDC's DATASTAT® can screen for 597 pairs of potentially severe adverse interactions to the FDA's "top 25" drugs prescribed for the elderly. The draft RFP's list of 231 drug interactions includes only 63, or 10.5 percent, of DATASTAT®'s 597 interacting pairs associated with the "top 25." Other weaknesses in draft RFP coverage of potentially serious problems associated with the FDA's "top 25" included:

- Lack of coverage for therapeutic duplicates;
- Dangers of exceeding maximum daily dosage;
- Potentially severe adverse reactions to allergies and cross sensitivities; and
- Precautions concerning drug-induced problems caused by drug interaction with specific diseases.

The chart on the following page provides a detailed graphic display of what is covered by NDC's DATASTAT®, and what was not covered by the draft RFP, concerning the "top 25" drugs prescribed for the elderly in 1986.

THE JOB AHEAD

NDC welcomes the opportunity and privilege to compete for Federal government contracts in the development and maintenance of Medicare's electronic point-of-sale and drug utilization review systems.

NDC's 4,000 employees and corporate officers are confident that our 15 years of experience in electronic drug utilization review will serve exceptionally well toward establishing and maintaining optimal quality assurance and economy in Medicare's forthcoming outpatient prescription drug benefit.

MEDICARE PROSPECTIVE DUR
AN ANALYSIS OF THE TOP 25 DRUGS PRESCRIBED FOR THE ELDERLY IN 1988

		POTENTIALLY SEVERE ADVERSE INTERACTION DRUG PAIRS		THERAPEUTIC DUPLICATE?		MAX DAILY DOSE?		ALLERGY CROSS-SENSITIVITY		DRUG DISEASE PRECAUTION	
	DRUG NAME	DRAFT RFP	NDC	DRAFT RFP	NDC	DRAFT RFP	NDC	DRAFT RFP	NDC	DRAFT RFP	NDC
1.	LASIX	NONE	60 pairs	No	Yes	No	Yes	No	Yes	No	Yes
2.	LANOXIN	2 pairs	31 pairs	No	Yes	Yes	Yes	No	Yes	No	Yes
3.	DYAZIDE	6 pairs	6 pairs	No	Yes	No	Yes	No	Yes	No	Yes
4.	DIGOXIN	2 pairs	30 pairs	No	Yes	Yes	Yes	No	Yes	No	Yes
5.	HYDROCHLOROTHIAZIDE	1 pair	31 pairs	No	Yes	No	Yes	No	Yes	No	Yes
6.	INDERAL	NONE	24 pairs	Yes	Yes	No	Yes	No	Yes	No	Yes
7.	ASPIRIN	2 pairs	63 pairs	Yes	Yes	No	Yes	No	Yes	No	Yes
8.	PERSANTINE	NONE	1 pair	No	Yes	No	Yes	No	Yes	No	Yes
9.	THEO-DUR	NONE	8 pairs	No	Yes	Yes	Yes	No	Yes	No	Yes
10.	NITROGLYCERIN	NONE	2 pairs	No	No	No	No	No	Yes	No	Yes
11.	INSULIN NPH	NONE	35 pairs	No	Yes	No	Yes	No	Yes	No	Yes
12.	COUMADIN	47 pairs	147 pairs	No	Yes	No	Yes	No	Yes	No	Yes
13.	PREDNISONE	NONE	42 pairs	No	Yes	No	Yes	No	Yes	No	Yes
14.	ALDOMET	NONE	3 pairs	Yes	Yes	No	Yes	No	Yes	No	Yes
15.	PROCARDIA	NONE	35 pairs	No	Yes	No	Yes	No	Yes	No	Yes
16.	ISORDIL	NONE	NONE	No	Yes	No	Yes	No	Yes	No	Yes
17.	MOTRIN	NONE	19 pairs	Yes	Yes	Yes	Yes	No	Yes	No	Yes
18.	TYLENOL w/CODEINE	NONE	NONE	No	Yes	No	Yes	No	Yes	No	Yes
19.	TAGAMET	3 pairs	22 pairs	Yes	Yes	Yes	Yes	No	Yes	No	Yes
20.	CARDIZEM	NONE	1 pair	No	Yes	No	Yes	No	Yes	No	Yes
21.	CAPOTEN	NONE	33 pairs	Yes	Yes	No	Yes	No	Yes	No	Yes
22.	TENORMIN	NONE	1 pair	Yes	Yes	No	Yes	No	Yes	No	Yes
23.	LOPRESSOR	NONE	1 pair	Yes	Yes	No	Yes	No	Yes	No	Yes
24.	TIMOPTIC	NONE	NONE	No	Yes	No	Yes	No	Yes	No	Yes
25.	ZANTAC	NONE	2 pairs	Yes	Yes	Yes	Yes	No	Yes	No	Yes

TOTAL PAIRS:	DRAFT RFP:	NDC:
	63 PAIRS	597 PAIRS

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United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

August 8, 1989

Mr. Dennis M. Styrsky (904 E)
Chief, Pharmaceutical Products Division
Department of Veterans' Affairs
Marketing Center
P.O. Box 76
Hines, IL 60141

Dear Mr. Styrsky:

On behalf of the Members of the Senate Special Committee on Aging, I am writing to express my appreciation for your participation in the Committee's July 18 hearing, "Prescription Drug Prices: Are We Getting Our Money's Worth?".

It was evident to all in attendance that you are a skilled manager who has much to teach the Congress regarding efficient governmental procurement of pharmaceutical products. As you could no doubt discern from the high level of interest of several Members of the Committee, your testimony was effective in establishing the potential for a wider role for the Department of Veterans Affairs in procuring prescription drugs for government agencies.

I was particularly interested in the portion of your statement devoted to explaining the Federal Supply Schedule (FSS) and differentiating it from the bulk-purchasing associated with the Depot system. In an attempt to clarify several issues regarding the FSS, I would like to request your answers to questions that have arisen since the hearing.

1. You said at one point in your statement that DVA recognizes the need for a "win/win" end result. Would you please elaborate on that statement for the record?

2. It is my understanding that through the FSS, DVA is procuring pharmaceuticals for several agencies of government, acting under a delegation of procurement responsibility from the General Services Administration. Your testimony states that the "Public Health Service was added to the agreement in 1984". Please explain the nature of this agreement, and supply the Committee with a copy of the agreement referred to in your testimony. If there is a specific statutory authorization for this agreement, please cite the appropriate section(s) for the Committee.

3. What is the approximate average volume of prescriptions annually filled by DVA's outpatient pharmacies? What is the range of annual volume at DVA's outpatient pharmacies (please supply figures representing the highest and the lowest prescription volumes)?

4. What is the approximate average volume of prescriptions annually filled by DVA's hospital inpatient pharmacies? What is the range of volume at DVA's hospital inpatient pharmacies (please supply figures representing the highest and the lowest prescription volumes)?

5. Given that under the FSS prescription drug products are delivered to individual DVA outpatient pharmacies and inpatient pharmacies "through commercial distribution channels", is DVA paying a higher price for prescription drug products that are delivered to (a) smaller (e.g. lower volume) pharmacy facilities, or (b) to pharmacies that are not associated with a hospital facility?

6. When asked during the hearing whether Medicare could achieve discounts like those DVA has achieved if it negotiated with manufacturers, you declined to speculate, stating that Medicare is "a different system". I have a different question for you. If DVA were to negotiate purchase prices on behalf of Medicare for an additional several hundred

million dollars worth of prescription drug products annually through the Federal Supply Schedule, do you believe DVA would continue to realize at least its present level of savings? Is it possible that this increased buying power would result in DVA realizing deeper discounts?

7. For each of the prescription drugs listed on the attached schedule, has DVA determined that another chemical entity (including those not listed on the attached schedule) is therapeutically equivalent? For example, are any of the anti-ulcer agents classified as "H2 antagonists" regarded by DVA as therapeutically equivalent? If no such determinations have been made, please explain why.

8. Has DVA ever employed the designation of therapeutic equivalence to obtain more favorable bids from manufacturers?

Once again, please accept my thanks for presenting the Committee with informative testimony on a very complex subject.

Sincerely,

David Pryor

David Pryor
Chairman

SINGLE SOURCE DRUGS

Brand Name (Generic Name)	Dosage Form
Axid (Nizatidine)	cap
Capoten (Captopril)	tab
Cardizem (Diltiazem)	tab
Feldene (Piroxicam)	cap
Lanoxin (Digoxin)	tab
Lopressor (Metaprolol)	tab
Naprosyn (Naproxen)	tab
Pepcid (Famotidine)	tab
Procardia (Nifedipine)	cap
Synthroid (Levothyroxine Sodium)	tab
Tagamet (Cimetidine)	tab
Timoptic (Timolol)	opth. soln
Transderm-Nitro (Nitroglycerin)	transdermal patch
Zantac (Raniditine)	tab

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United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

August 17, 1989

Mr. William Mincy
Partner
The Lenco Group
2858 Remington Green Circle
Suite 102
Tallahassee, FL 32308

Dear Mr. Mincy:

I am writing to thank you for your fine contribution to the Special Committee on Aging hearing, "Prescription Drug Prices: Are We Getting Our Money's Worth?", held July 18, 1989. Your extensive knowledge of the problems and opportunities faced by pharmacists who seek favorable wholesale prices from drug manufacturers provided Members of the Committee with a rare glimpse of actual conditions in the market today.

Further evidence of the Committee's interest in capitalizing on your expertise is embodied in the following questions, suggested by Members after the hearing. If you would be so kind as to submit written replies to these questions, your answers will be incorporated into the official hearing record.

1. To what extent do volume purchases by pharmacies or their buying groups affect price? How effective, as measured by manufacturers' willingness to discount their drug prices, are volume discounts in relation to other market strategies employed by various buyers of prescription drugs?

2. What effect, if any, is the Robinson-Patman Act having on retail pharmacists?

3. What effect, if any, has the Robinson-Patman Act had on the ability of "non-profit" entities to purchase drugs from manufacturers (either directly or through wholesalers) at a discount?

4. To what extent are pharmacy buying groups involved in brokering of price discounts, relative to the entire retail market for prescription drugs?

5. In your opinion, would it be feasible for Medicare and/or Medicaid to employ strategies similar to those used by major buying groups, for example, by paying the Average Wholesale Price to pharmacists while obtaining a previously negotiated rebate from manufacturers?

6. In your experience, relative to the published Average Wholesale Price, what is the difference between prescription drug prices charged by manufacturers to retail pharmacy chains (e.g., Peoples Drug) and independent retail pharmacists (e.g., Wall Drug, in Wall, South Dakota)?

If you should have any questions regarding this letter, please contact David Schulke of the Aging Committee staff at 202-224-5364. Once again, on behalf of the Members of the Committee, I would like to thank you again for your testimony and continued assistance.

Sincerely,

David Pryor

David Pryor
Chairman

DP:ds

Robert F. Allnutt
EXECUTIVE VICE PRESIDENT

Pharmaceutical
Manufacturers
Association

August 17, 1989

The Honorable David H. Pryor
Chairman
United States Senate Special
 Committee on Aging
Washington, D.C. 20510-6400

Dear Mr. Chairman:

In Gerry Mossinghoff's absence, I have enclosed eight Answers for the Record that he said he would provide during the hearing held by the Senate Special Committee on Aging on July 18 on prescription drug prices.

We also have undertaken a review of the benefits of the New Molecular Entities included in the tabulation of "New Drug Approvals" prepared by the Committee staff for the hearing. We will provide you with the results of our study as soon as it is completed.

Please let me know if you have any questions or if we can be of help in any other way.

Sincerely yours,

Robert F. Allnutt

Enclosures

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Office of Acquisition
and Materiel Management

Washington DC 20420

Veterans
Administration

AUG 30 1989

Aging

In Reply Refer To: 94

Honorable David Pryor
United States Senate
Special Committee On Aging
Washington, DC 20510-6400

Dear Senator Pryor:

Enclosed are the responses to the additional questions raised by the Special Committee on Aging and sent in your letter dated August 8, 1989, to the Chief, Pharmaceutical Products Division, VA Marketing Center.

We appreciate the opportunity to contribute to the inquiries related to the cost of pharmaceutical products.

Sincerely,

H. ROBERT SALDIVAR
Deputy Assistant Secretary for
Acquisition and Materiel Management

Enclosures

1. You said at one point in your statement that DVA recognizes the need for a "win/win" end result. Would you please elaborate on that statement for the record?

A. All successful negotiators believe that both parties to the process must be satisfied with the outcome. Recognizing the magnitude of the drug procurement program and the costs associated with it make us fully aware of the need to be forceful negotiators. We also realize the importance of having the manufacturer agree upon a price they also consider to be "fair and reasonable" for the way we are buying relative to their other customers. A negotiation that is so one sided as to have one party gaining everything at the expense of the other party will only occur one time. A "loser" in negotiations will either be the big winner in the next contract or will not come back to the bargaining table. Negotiations require compromise by both parties to the agreement. This is what we strive for in our contracting efforts.

2. It is my understanding that through the FSS, DVA is procuring pharmaceuticals for several agencies of government, acting under a delegation of procurement responsibility from the General Services Administration. Your testimony states that the "Public Health Service was added to the agreement in 1984". Please explain the nature of this agreement, and supply the Committee with a copy of the agreement referred to in your testimony. If there is a specific statutory authorization for this agreement, please cite the appropriate section(s) for the Committee.

A. The Interagency Agreement, dated June 26, 1984, as amended, to add the Public Health Service, covers the shared contract responsibility between Department of Veterans Affairs, Department of Defense and the Public Health Service. It specifically involves those pharmaceutical and medical items that are maintained in the respective depot systems. The contracting responsibility has been divided between the DoD and DVA with the Public Health Service assuming limited contracting for specific items such as child immunization vaccines. The agreement was entered into under the authority of the Economy Act of June 30, 1932, as amended (31 U. S. C. 1535). A copy of the agreement is provided as you requested.

INTERAGENCY AGREEMENT
BETWEEN THE
U.S. PUBLIC HEALTH SERVICE
DEPARTMENT OF HEALTH AND HUMAN SERVICES
THE
DEPARTMENT OF DEFENSE
AND THE
VETERANS ADMINISTRATION

I. PURPOSE.

To formalize an agreement between the U.S. Public Health Service (PHS) - Department of Health and Human Services (DHHS), the Department of Defense (DoD), and the Veterans Administration (VA), whereby DoD and VA will include PHS requirements for medical items approved for purchase under respective shared procurement consolidated contracts. Under this agreement, the Health Resources and Services Administration (HRSA), acting for the Public Health Service as the lead agency, will be authorized to process delivery orders against these contracts for shipment of their requirements to designated supply depots.

II. BACKGROUND.

A. In January 1978, the Office of Federal Procurement Policy, Office of Management and Budget, issued a memorandum to DoD, VA, DHHS (then DHEW) and GSA which assigned the lead role to DoD and VA for developing a program for improving the purchase and management of medical items. This assignment established the requirement for an equitable division of medical items between DoD and VA to eliminate duplication of procurement effort by the federal government at the central level for the same items.

B. In June 1978, an interagency agreement between the DoD and VA established requirements for dividing purchasing responsibility, developing a joint item entry control system, and establishing procedures to review, simplify and eliminate the multiplicity of specifications.

C. Under the shared procurement concept, the purchasing roles of DoD and the VA involve preparation of product descriptions, determination of contractor responsibility, and timely award and administration of contracts for products covered by this agreement in accordance with the laws and regulations governing Federal purchasing. Accordingly, the DoD and VA contracting officers are the only officials empowered by law to make interpretations and resolve disputes concerning the performance of their respective contracts.

III. RESPONSIBILITIES.

A. DoD and VA agree:

(1) To include PHS estimated annual requirements for medical items in their respective shared procurement contracts with a provision authorizing HRSA to process delivery orders for shipment to designated supply depots.

(2) To provide PHS a copy of their respective solicitations when PHS requirements are included.

(3) To notify HRSA within twenty four (24) hours of contract awards which include PHS requirements.

(4) To send HRSA one completed copy of the contract after contract award when PHS requirements are included.

B. PHS agrees:

(1) To provide a complete listing of the medical items it currently procures and stocks to the DoD and VA for evaluation and assignment to the appropriate agency for procurement.

(2) To furnish required data to DoD and VA upon request by the appropriate procuring activity.

(3) To furnish the requirements of paragraph III, B. (1) and (2), within the time frames as established jointly with the DoD and VA contracting officials.

(4) To provide an appropriate representative to serve on the Interagency Medical Procurement Management Committee. This committee is established to oversee shared procurement activities.

(5) To provide a representative to serve as PHS coordinator for the shared procurement program. This representative will be required to maintain close liaison with the VA Coordinator and the DoD Program Manager regarding shared procurement activities.

(6) To provide appropriate representatives to serve on established committees of the Shared Procurement Program Task Group. These committees provide an interface between participating agencies for procurement, review, coordination and market research of medical products.

C. All parties agree:

Not to take unilateral action without prior coordination on any data, e.g., exceptions, deviations, waivers, FDA certifications, etc.

IV. SHARED PROCUREMENT COORDINATORS.

A. DoD:

Mr. Paul Bellino (DPSC-AV)
DoD Shared Procurement Program Manager
Directorate of Medical Materiel
Defense Personnel Support Center
2800 South 20th Street
Philadelphia, PA 19101
Telephone: (215) 952-4350

B. VA:

Mr. James M. Jeffries, Jr. (91)
Supply Management Representative
Policy and Interagency Service
Office of Procurement and Supply
Veterans Administration
810 Vermont Avenue, N.W.
Washington, D.C. 20420
Telephone: (202) 389-2856

C. PHS:

Mr. Harry O. Knutson
Chief, Materiel Management Branch
Division of Grants and Procurement Management
Health Resources and Services Administration
5600 Fishers Lane
Rockville, Maryland 20857
Telephone: (301) 443-1436

V. PERIOD OF AGREEMENT.

This agreement is effective upon the signature of the parties below, with no expiration date, and may be terminated upon a 180 day written notice to the other parties.

VI. AMENDMENTS.

Revisions to this agreement may be developed at any time by the participants. Such revisions shall become effective on such date as is mutually agreed upon by all parties. The agreement will be reviewed for adequacy and effectiveness at least annually and renegotiated as necessary.

VII. AUTHORITY.

This agreement is entered into under the authority of the Economy Act of June 30, 1932, as amended (31 (U.S.C. 1535).

APPROVED AND ACCEPTED FOR
THE DEPARTMENT OF DEFENSE

BY: Robert W. Daniel Jr.
Robert W. Daniel, Jr.
Deputy Assistant Secretary of Defense
(Logistics and Materiel Management)

DATE: 5 JUN 1984

APPROVED AND ACCEPTED FOR
THE VETERANS ADMINISTRATION

BY: Clyde C. Cook
CLYDE C. COOK
Director
Office of Procurement and Supply

DATE: June 7, 1984

APPROVED AND ACCEPTED FOR THE
HEALTH RESOURCES AND SERVICES ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

BY:
JOHN H. KELSO
Acting Administrator

DATE: [illegible]

APPROVED AND ACCEPTED FOR THE
U.S. PUBLIC HEALTH SERVICE
DEPARTMENT OF HEALTH AND HUMAN SERVICES

BY:
WILFORD J. FORBUSH
Deputy Assistant Secretary
for Health Operations

DATE: June 26, 1984

3. What is the approximate average volume of prescriptions annually filled by DVA's outpatient pharmacies? What is the range of annual volume at DVA's outpatient pharmacies (please supply figures representing the highest and the lowest prescription volumes)?

A. The approximate yearly outpatient prescription volume for Veterans Health Services and Research Administration (VHS&RA) is 57,000,000 according to FY 1988 data. The volume range for VHS&RA outpatient pharmacies using FY 1989 data* will be 8500 prescriptions per year for the lowest to 1,100,000 per year for the highest.

*figures based on projections made using second quarter data

4. What is the approximate average volume of prescriptions annually filled by DVA's hospital inpatient pharmacies? What is the range of volume at DVA's hospital inpatient pharmacies (please supply the figures representing the highest and the lowest prescription volumes)?

A. This question asks for data on inpatient prescriptions. VA pharmacies dispensed 993,801 inpatient prescriptions in FY 1988. However, the number of inpatient prescriptions filled by the VA are insignificant and do not represent the major workload indicator for VA inpatient pharmacies. Inpatient workload is traditionally measured by doses. The VA dispensed over 168 million oral unit doses, 73 million ward stock doses, and 10 million intravenous piggyback doses in FY 1988. Additionally, 375 thousand hyperalimentation solutions, 2 million admixtures, and nearly 12 million fluids and administration sets were dispensed in FY 1988. As a key indicator variable, the volume range for inpatient unit dose are 4 million doses at the highest range and 100 thousand at the lowest range.

5. Given that under the FSS prescription drug products are delivered to individual DVA outpatient pharmacies and inpatient pharmacies "through commercial distribution channels", is DVA paying a higher price for prescription drug products that are delivered to (a) smaller (e.g., lower volume) pharmacy facilities, or (b) to pharmacies that are not associated with a hospital facility?

A. The primary objective of the Federal Supply Schedule program is to negotiate the contract for all of the government's requirements (i.e., total dollars) as a single customer. Under this premise there is one price for all ordering offices, regardless of size or the volume they purchase as an individual entity. To provide benefits for the larger ordering offices we are constantly attempting to negotiate quantity or tiered pricing which affords greater discount for quantity purchases.

6. When asked during the hearing whether Medicare could achieve discounts like those DVA has achieved if it negotiated with manufacturers, you declined to speculate, stating that Medicare is "a different system". I have a different question for you. If DVA were to negotiate purchase prices on behalf of Medicare for an additional several hundred million dollars worth of prescription drug products annually through the Federal Supply Schedule, do you believe DVA would continue to realize at least its present level of savings? Is it possible that this increased buying power would result in DVA realizing deeper discounts?

A. While at first blush it might appear the obvious answer to this question is greater discounts should be realized, it is not that simple. This question is quite complex and subject to many variables beyond increased purchasing or contracting volume. It is difficult to put into perspective the inherent problem associated with Federal Supply Schedule contracting. One of the greatest obstacles is related to the issue of treating government as a single customer when there are more than 3,000 ordering offices and hundreds of paying activities. To deal with the question of adding dollar volume to the schedule is only half of the negotiation. If we were asked to add Medicare in a very broad sense that would make virtually every pharmacy in the nation an authorized user of the Federal Supply Schedule, I seriously doubt it would increase negotiating leverage and would more than likely reduce our effectiveness. Conversely, should Medicare have centralized ordering activities established that were under government control and possibly regionalized there could be a significant benefit in the added volume to FSS. The nature of the industry and its relation with the federal market would almost mandate government operation of Medicare ordering. The open-endedness of this question makes it most difficult to answer because of all the possible variables that could impact either in a positive or negative way.

7. For each of the prescription drugs listed on the attached schedule, has DVA determined that another chemical entity (including those not listed on the attached schedule) is therapeutically equivalent? For example, are any of the antic-ulcer agents classified as "H2 antagonists" regarded by DVA as therapeutically equivalent? If no such determinations have been made, please explain why.

A. The Department of Veterans Affairs (VA) has made no national determinations of therapeutic equivalence. Decisions regarding therapeutic equivalency are made at the local medical center based on a decision by the Pharmacy and Therapeutics (P&T) Committee as a part of the formulary management process.

Historically, activities to control pharmaceutical expenditures in the VA have been based on locally-managed formulary actions such as strict formulary enforcement, restriction of the prescribing of high cost pharmaceuticals to clinical experts, prospective review of medication orders against appropriateness protocols approved by the P&T Committee, and increased vigilance on the part of the P&T Committee in controlling the numbers of therapeutically equivalent items on the local formulary.

The cost of newer, more expensive pharmaceuticals and increased workload place increasing fiscal demands on the medical care budget. This has resulted in the VA exploring other options to control pharmaceutical expenditures. One option which is currently being explored is drug standardization (a National Core Formulary). Five medications have been selected for the initial test phase. This initiative has the potential to lead to a true national formulary which incorporates the concepts of therapeutic equivalency.

The mechanism for implementation of a true national formulary system utilizing therapeutic equivalency concepts must include enough flexibility to allow variations in local medical practice based on patient needs.

8. Has DVA ever employed the designation of therapeutic equivalence to obtain more favorable bids from manufacturers?

A. As the Department of Veterans Affairs (VA) has not made any national determinations of therapeutic equivalents, there has been no national action by VA to obtain more favorable bids from manufacturers.

The VA is currently testing the concept of standardization through a National Core Formulary. Five medications have been selected for the initial test phase. Additionally, another 50-100 pharmaceuticals are in the process of being identified for incorporation into the standardization process. This initiative has the potential to lead to a true national formulary system which may utilize the concept of therapeutic equivalency.

Jerry L. Schwartz, Dr.P.H.
746 Hawthorn Lane
Davis, CA 95616

November 3, 1989

Senator David Pryor, Chairman
U.S. Senate Special Committe on Aging
Rm. G-31, Dirksen Senate Office Building
Washington, DC 20510

Dear Mr. Chairman and Members of the Committee:

This information addresses the issue of drug pricing and, specifically, the outrageous profiteering by Somerset Pharmaceuticals, Inc., in their pricing of deprenyl (Selegiline) sold under the brand name ELDEPRYL. The information is supplied at the request of David Schulke, the Chief of Oversight for the Committee.

Eldepryl was approved by the FDA in June for the treatment of Parkinson's disease. I wouldn't be surprised if the production cost is around 10 cents per tablet. Eldepryl is being sold for between $2.00 and $2.50 per tablet.

Description and Action of Deprenyl

Deprenyl was discovered in Budapest, Hungary, in 1964 by J. Knoll. It is produced by CHINOIN Chemical & Pharmaceutical Works, Budapest, Hungary. It has been used in Europe for Parkinson patients for about 15 years. Sale of deprenyl began in Hungary in 1981 as JUMEX, in Great Britain in 1982 as ELDEPRYL, and in Austria in 1983 as JUMEX. It is called JUMEXAL in Switzerland and MOVERGAN in Germany. (Deprenyl, Eldepryl, and Jumex will refer to the same 5 mg tablet.)

Current evidence indicates that symptoms of Parkinson's disease (PD) are related to the depletion of dopamine in the corpus striatum. The most widely used and accepted basic treatment of PD is the use of levodopa together with carbidopa, a peripheral decarboxylase inhibitor. The combined pill is called Sinemet. However, the effectiveness of Sinemet declines after long term use. As a result, dosages of levodopa are increased and side effects increase in severity.

The concomitant use of drugs that inhibit the monoamineoxydase (MAO) enzyme that normally inactivates dopamine, appears to be a logical strategy to maintain the desirable levels of dopamine product in the brain. However, the use of nonselective MAO inhibitors with levodopa could produce clinically dangerous hypertensive crisis.

There are two forms of MAO, type A and B, which differ in their substrate specificity. MAO-A preferentially oxidizes serotonin and noradrenaline, while MAO-B generally acts upon phenylethylamine and benzylamine. Selegeline (deprenyl) is a highly potent selective MAO-B-inhibitor which preserves dopamine, and enables levodopa to supply dopamine more effectively and at a lower dose. This in turn decreases the dose-related side effects known to accompany levodopa therapy.

In summary, Eldepryl conserves dopamine by inhibition of the enzyme monoamine oxidase (Type B) which rapidly inactivates dopamine in the brain. Eldepryl also inhibits the dopamine reuptake storage mechanism and thus permits the available dopamine to be used more efficiently. The addition of Eldepryl to a levodopa regimen can reduce the amount of levodopa required by as much as 25 percent. Eldepryl, used in combination with levodopa, also helps to reduce the frequency and severity of hypokinetic/akinetic disabilities such as "wearing-off" or "end of dose" deterioration and early morning akinesia.

No serious or irreversible side-effects have been observed, nor do tolerance or dependence occur with the use of deprenyl. It is a MAO inhibitor without the "cheese effect" in therapeutic dose of 10 mg. daily. Thus, it can be safely taken without dietary restrictions.

Cost of Deprenyl

I have Parkinson's disease and began taking Sinemet (levodopa + carbidopa) and deprenyl in 1986. I have been purchasing Jumex by mail from a pharmacy in Vienna, Austria. I was paying 458 Austrian shillings for a bottle of 50 tablets which, at the July 1989 dollar exchange, was $68.88 for 100 tablets or 69 cents per pill. The price was increased in 1989 by the Austrian pharmacy to 511.50 AS, which cost $76.93 per 100 pills or 77 cents per pill. I also paid postage.

A friend purchased Jumex (5 mg) for me in Rome two different times for a cost of around $44 for 100 pills. Chiesi Farmaceutici markets Jumex in Italy. The price is printed on the package as 28,595 lira for 50 tablets for "assisted patients" plus 3,000 lira for nonassisted patients. According to the dollar exchange rate, the price would be $40-42 for assisted patients and around $45 for nonassisted patients. (A man in Davis, told me that his brother bought 1,000 Jumex tablets at a pharmacy in Vatican City for $333 or 33 cents per pill.)

COST FOR DEPRENYL PER 5 mg TABLET AT U.S. AND FOREIGN PHARMACIES

(All prices are in U.S. dollars and cents at current exchange rate)

	Cost per tablet when purchasing		
Location of pharmacy	60 tablets	100 tablets	120 tablets
Rome, Italy		.41 to .46	
Vienna, Austria		.79	
Toronto, Canada		1.00 to 1.12	
Davis, California			
Davis Med. Center	2.38	2.38	2.38
Quessenberry	2.43	-	2.28
Payless (chain)	2.08	2.08	2.08
Long's (chain)	2.00	1.96	1.95
Mail Order			
RX Allstates, Chicago	1.73	1.69	1.69
Pharmail, Champlain, NY	1.83 to 2.00 (price not decided)		

Some people were purchasing Eldepryl from Deprenyl Research Limited, Toronto, Canada, for around $1.00 to $1.12 per pill. Deprenyl Research Limited has informed its U.S. customers that they can no longer sell to U.S. customers due to an agreement with Somerset Pharmaceuticals to restrict sales to Canada.

I telephoned Davis pharmacies to find out their prices for Eldepryl. Two of the pharmacies were regular and two were chains that discount their prices. The table on page 2 summarizes the cost of deprenyl in Davis (CA), Rome, Vienna, Toronto, and two mail order pharmacies located in Chicago and Champlain, NY.

If Eldepryl (per 5 mg tablet) costs 45 cents in Italy, 79 cents in Austria, and $1.00 in Canada, why should it cost up to $2.43 in the United States?

The reason is profiteering. The S.C. Johnson Company had the rights to Eldepryl. In 1986, senior management formed Somerset Pharmaceuticals, Inc. and purchased the Johnson ethical pharmaceutical assets in order to market Eldepryl. Somerset is located in Denville, NJ. Donald A. Buyske is Chairman and Taylor H. Maxwell is President.

Patients will be taking two 5 mg pills per day. The cost will be around $1,700 per year or $142 per month at a regular pharmacy, and $1,460 per year or $122 per month at a chain pharmacy. Mail order costs would be $1,234 per year or $103 per month. Austrian prices are about one-third: $576 per year or $48 per month. In Italy, the cost would be around $321 per year or $27 per month.

Somerset's Pricing of Eldepryl is Outrageous

Eldepryl is a valuable drug for Parkinson's Disease; it will be widely prescribed. There are indications that if Eldepryl is started early in the disease, it can slow the progression of the disease. Many patients will not be able to pay the price charged for the drug. The price that Somerset is charging is an outrage! I believe the only costs Somerset had were getting it through the FDA, the expenses of forming a new company, and purchasing the pharmaceutical assets. The pills are produced in Hungary and the cost after all these years should be minimal.

Why should health plans and insurers, Medicare, Medicaid, and Parkinson patients get roasted? These high prices will raise the cost of health care. Somerset officers should reveal their costs and pricing policy.

I compliment the Committee for looking into drug pricing. High costs of essential drugs create a burden for consumers, government, and health plans. If the Committee wishes to contact me for further information, I would be pleased to oblige. My telephone number is (916) 756-5196.

Sincerely,

Jerry L. Schwartz

DAVID PRYOR, ARKANSAS, CHAIRMAN

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United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400
November 9, 1989

Mr. Richard Michael Berryman
Director of Pharmacy
Community Memorial Hospital
126 Buena Vista Circle
South Hill, VA 23970

Dear Mr. Berryman:

On Thursday, November 16, 1989, the Senate Special Committee on Aging will convene its second public hearing on the subject of prescription drug manufacturer pricing policies and practices. I am writing to invite you to testify at this hearing.

This hearing will explore opportunities in the current marketplace for Medicaid programs, service providers and others to negotiate lower prescription drug purchase prices with manufacturers. The Committee is interested in learning about possible models for bringing manufacturers to the bargaining table, and in identifying actions of manufacturers which may have thwarted previous attempts at such negotiations.

Specifically, the Committee would like you to address the following issues and questions in your testimony:

1. Please describe your role as Chairman of the Virginia State Medicaid Board, and the problems facing the State Medicaid program.

2. Given that pharmaceutical costs generally amount to less than 10% of medical expenditures, why is the State of Virginia seeking reductions in expenditures for prescription drugs?

3. What options is the State considering in its bid to lower prescription drug costs, and what have been the responses of pharmacists and pharmaceutical manufacturers to these proposals?

4. Because of your unusual dual role as a community pharmacist and as a hospital pharmacist, you may have observed differences in wholesale prices available in each setting. If so, have you attempted to secure lower wholesale prices for your community pharmacy, and what has been the response of the manufacturers you have sought to negotiate with?

5. Some have suggested that State Medicaid programs should negotiate prescription drug prices with manufacturers, pay each pharmacist the usual "Average Wholesale Price" and dispensing fee, and then invoice manufacturers for a "rebate" or "chargeback" to account for the negotiated discount. Do you recommend that Congress work with States to negotiate lower prescription drug prices through such a "chargeback" or "rebate" program?

Please provide the Committee with 150 copies of your written statement on Tuesday November 14, 1989. The hearing will commence at 9:30 a.m. on November 16, 1989, in Room SD-628 of the Dirksen Senate Office Building. On the morning of the hearing, please check in at the Committee office in Room G-31 of the Dirksen Senate Office Building between 8:45 and 9:15 a.m. If you should have any questions regarding this invitation, please contact David Schulke of the Special Committee on Aging staff at 224-5364.

Sincerely,

David Pryor

David Pryor
Chairman

Enclosure
DP:dgs

ICN Pharmaceuticals, Inc.

3300 Hyland Avenue
Costa Mesa, California 92626
Telephone: (714) 545-0100
Telex: 67-0413

November 15, 1989

Senator David H. Pryor
Chairman
U.S. Senate Special Committee on Aging
267 Senate Russell Office Building
Washington, D.C. 20510-0402

Dear Sen. Pryor:

ICN Pharmaceuticals is a small, California-based pharmaceutical company that makes, markets and sells 300 pharmaceutical products in the United States and internationally. The company has been in business for 30 years and over this period has developed and gained commercial authorization to market a number of useful therapeutic compounds. The company is research-based and over the past decade has invested over $150 million in research and development for new pharmaceuticals, principally antivirals.

ICN is a socially responsive company whose main mission is to improve the health of mankind through the development and distribution of useful pharmaceutical therapies. This is embodied in the company's motto: "He who has health has hope and he who has hope has everything." As the founder of the company and an immigrant who fled from communism, I have a profound belief and respect for the American political system, and welcome the opportunity to respond to any and all questions that have been asked of us by the committee staff on our marketing practices for the drug Mestinon. My only regret is that due to the distance involved and the short notice of the hearing we received, I am unable to appear in person.

In line with the company's philosophy, let me say immediately at the outset that it is the company's policy that no patient will ever be denied a drug marketed by ICN because of his or her inability to pay. This policy applies to Mestinon, which is used in the chronic treatment of Myasthenia Gravis. ICN maintains an indigent patient program whereby patients can obtain Mestinon free of charge. Any patient who is not able to afford their medication, who does not have health insurance, or who has had Mestinon purchases rejected for coverage by their health insurance can receive their drug free of charge. Currently, 285 patients, representing approximately five percent of all Mestinon-treated patients, receive their drug at no charge through this program.

Our indigent program is very simple. All a patient has to do is give us a request signed by the patient and his or her physician. In some instances, a copy of the patient's health plan indicating it doesn't cover prescriptions is needed. We don't check further. No questions asked.

The committee staff has expressed interest about Mestinon, its price and the way the drug is marketed. The most useful way to respond to these areas of inquiry is to recount ICN's history with the drug to date.

At the time, ICN's hospital sales force had only one product to sell, an antiviral agent used in the treatment of hospitalized infants with severe respiratory disease. As part of a strategy to increase the number of products marketed by the company's hospital sales force, ICN acquired the U.S. marketing rights to Mestinon from F. Hoffmann-La Roche & Co. in June of 1988. The addition of products like Roche's line of anticholinesterase products, of which Mestinon is a part, makes the sales force more cost-efficient by spreading overhead over more products. This makes it more economical to maintain a hospital sales force.

ICN's licensing strategy is based on licensing products with smaller sales volumes. Simply put, we believe it makes more sense for small companies to handle smaller products and bigger companies to handle larger products. Big companies are better equiped to maintain large national and international distribution systems for products with large patient bases. Small products often get lost in larger companies. Big companies often do not pay much attention to smaller products. Small companies can.

Mestinon is a case in point. It is a drug of longstanding that is used to currently treat a total population of only approximately 7,500 patients in the U.S. The average cost of Mestinon approximates $600 a year. In November of this year, a price increase of 8 percent was announced by the company. While we cannot address the pricing history of this drug before we obtained our licensing rights, this will be the first price increase in the 16 months since ICN assumed U.S. marketing rights.

Although the 8 percent increase approximates inflation, it was really intended to offset the cost of capital improvements necessary for ICN to produce Mestinon. It also allows us to initiate research into new uses for Mestinon. Through this effort, myasthenia gravis patients, as well as patients in an entirely different disease category, may ultimately benefit from the fruits of this research. Moreover, the price increase allows the company to produce and distribute an educational videotape to physicians, such as opthomologists, most likely to encounter undiagnosed patients early in their disease. We believe that half the actual number of myasthenia gravis cases in the U.S. are currently undiagnosed.

The committee staff has asked why the drug bank contracts were allowed to expire. In essence, the drug banks involve a two-tier pricing system. Following a review of the drug bank system in July of 1988, we determined that this pricing strategy was not conducive to the way ICN believes it should conduct its business. Our policy is to have one price for each of our products to the same class of customers. Under the two-tiered pricing system in effect under the drug banks, local drug stores are at a competitive disadvantage to larger institutions receiving price breaks under the "drug bank" system. This is not consistent with the American economic system and it is against our general business policy as a company.

Ninety percent of patients in the drug banks are covered by private and public health care plans. Because we recognized that the expiration of the drug bank contracts could possibly provide hardship to some, we provided a grant to Myasthenia Gravis Foundation, part of which was to be used to subsidize patients using the drug banks. Most important, the indigent program is open to all patients, including former drug bank users.

Since acquiring the licensing rights, we have attempted to work closely with the Myasthenia Gravis Foundation. We have repeatedly asked the foundation for suggestions as to what contributions the company can make toward helping for the care and treatment of Myasthenia Gravis patients. Consequently, a $50,000 grant was awarded to the foundation in 1989 to support patient services, public and medical education and research. This grant is intended to be ongoing and the amount of future installments is currently under review.

In summary, since the company obtained licensing rights to Mestinon, ICN has had concern that some patients, particularly those on fixed incomes without health insurance, may find it difficult to afford the drug. In order to avoid placing undue burden on these patients and any other patients who, for whatever reason, may feel a financial strain in obtaining their medication, ICN has made and will continue to make Mestinon available at absolutely no charge. We believe this action meets the needs of all Myasthenia Gravis patients, and is in line with our general corporate philosophy and the country's health care objectives.

We would be more than happy to answer any questions raised by the contents of this letter as well as to continue further dialogue with the Myasthenia Gravis Foundation in the interest of MG patients.

Sincerely,

Milan Panic

Milan Panic
Chairman and Chief
Executive Officer

MP:sab

11/16

Elizabeth R. Prichard
510 E. 86 Street, Box 44
New York, New York 10028

Senator David Pryor, Chairman
U.S. Senate Special Committee on Aging

Dear Senator Pryor,

There is urgent need for federal legislation to regulate the amount of increase in cost of medications, especially maintenance drugs for the chronically ill. Children, adults and the aged are all affected.

Excessive increases in the cost of Mestinon, the most widely prescribed medication for treatment of Myasthenia Gravis, an auto-immune neuromuscular chronic disease is an illustration. Myasthenia Gravis can affect persons from infancy to old age, many are older men. It affects persons of all races and in all parts of the world.

In 1988 the cost of a bottle of 500 Mestinon 60mg rose here in New York City from $90 to $148.75 and in one supposedly cut rate store, $170 with a discount of 10% for seniors. Now an increase of 8% has been announced. Many Myasthenics must take 18-20 pills a day on a 24 hour basis, with some 30 pills a day. In addition many must also take Mestinon Timespan which costs around $75 for 100 pills. Some Myasthenics must also take Imuran, Prednisone and others. Some now in their old age have been taking Mestinon since they were young and thus able to work, raise families. It is an expensive disease. A member of my family has Myasthenia Gravis.

Mestinon produced by Hoffman LaRoche is distributed solely in this country by ICN, a California concern. Thus the patient has no selection in purchasing this life sustaining drug.

As the result of excessive increases and which may continue-

1. Many will not be able to afford the medication which enables them to function, or take less thus limiting their ability to function, and become invalids
   a. Further financial drain on a family, resulting in serious deprivations on other family members.
   b Hospitalization will be necessary for many, often periodically when unable to breathe.
   c. Nursing home placement for some often at public expense.
2. Increased health care costs.

Without federal regulations there will be no stoppage in further increases.

Sincerely,

Elizabeth R. Prichard

November 12, 1989

Pharmaceutical
Manufacturers
Association

Gerald J. Mossinghoff
PRESIDENT

November 15, 1989

The Honorable David Pryor
Chairman
Select Committee on Aging
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

At the July 18 hearing of the Special Committee on Aging relating to prescription drugs, you released a staff briefing paper that regrettably, and erroneously, asserts that most of the research done by America's pharmaceutical industry is of little value and that most of the new drugs approved by the Food and Drug Administration are of "little or no" significance. As I said at the hearing, that conclusion cannot be sustained by the facts.

The enclosed report, AMERICA'S PHARMACEUTICAL RESEARCH COMPANIES -- A COST-EFFECTIVE SOURCE OF IMPORTANT NEW MEDICINES, shows that contrary to the "findings" of the staff, industry research and development produces significant new medicines and reduces the overall cost of medical care. For example, the U.S. leads in the discovery of "world class" drugs, originating nearly half of the new medicines that achieved worldwide acceptance between 1975 and 1986.

The staff calls its analysis of research and development output the "me-too factor." If one were to accept the staff's view, nearly half of the drugs which the World Health Organization says are essential for health in every country in the world would be considered of little or no value. I am also enclosing a recently published article by the Center for the Study of Drug Development at Tufts University that concludes:

> "Nearly one-half of the drugs present on the WHO essential drug list are available as a result of me-too research, and nearly one-quarter of the therapeutic indications described by the WHO essential drug list are treated by drugs originally indicated to treat some other disease or condition."

As the Special Committee on Aging continues its inquiry concerning prescription drugs, I urge you to consider the facts rather than the flawed conclusions of the Committee majority staff.

Sincerely,

Gerald J. Mossinghoff

Enclosures

1100 Fifteenth Street NW, Washington, DC 20005 • Tel: 202-835-3420 • FAX: 202-835-3413, 3414

The World Health Organization's Essential Drug List

The Significance of Me-too and Follow-on Research

Linda J. Wastila, B.S. Pharm., M.S.P.H., Marianne E. Ulcickas, B.S., and Louis Lasagna, M.D.

The Center for the Study of Drug Development, Tufts University, Boston, Massachusetts

ABSTRACT: Third-world health-advocacy organizations have criticized the pharmaceutical industry for expending excess effort in patenting modifications and new uses of already existing drugs rather than focusing their resources on developing innovator drugs. These groups contend that such "me-too" and "follow-on" research yields drugs with little or no therapeutic value over innovator drugs and that underdeveloped nations suffer from this insignificant research. In order to examine this charge, we reviewed the 1987 World Health Organization's (WHO) Essential Drug List to determine the extent to which innovator drug use is advocated. Analysis of 195 listed drugs representing 236 therapeutic indications reveals that nearly 50% of the drugs recommended by the WHO are not the innovator drugs of their respective classes. Additionally, nearly 25% of drugs on this list are included for therapeutic uses approved subsequent to the initially approved indication(s). These findings suggest that research dedicated to improving efficacy and safety profiles of innovator drugs, as well as discovering new therapeutic uses, is of medical importance to both developed and underdeveloped nations.

Key Words: *World Health Organization; Me-too drugs; Essential drugs; Molecular modification.*

INTRODUCTION

In the pharmaceutical industry, as in most health-related businesses, there is a conflict between the altruism expected of the industry and the industry's desire to maximize profits. Observers have, from time to time, criticized the number and types of drugs marketed, the associated costs, and the research motives and methods employed to develop drugs [1–3]. One of the most contentious of these criticisms is the driving force that profit motivation plays in a drug firm's decision to undertake a particular direction in research and development.

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In 1967, President Johnson charged the newly established Task Force on Prescription Drugs to undertake a comprehensive study of the problems associated with the inclusion of prescription drugs as a Medicare benefit. In its *Final Report*, published in 1969, one of the major concerns expressed by the committee was the overabundance of "duplicative, noncontributory" drugs produced by pharmaceutical firms [4]. For the most part, these drugs were characterized as molecular modifications, or "me-toos," of older drugs available on the market. Although concern about molecular modification research was noted first in 1961 Senate hearings, it was the *Final Report* that popularized the term "me-too" [5]. Five years later, in their book *Pills, Profits and Politics*, former Task Force members Silverman and Lee further emphasized their concern about me-too research [1]:

> Most molecular modifications have yielded only me-too products. The impact of the drug deluge on physicians—and therefore their patients—has long been a matter of serious concern. It is difficult to comprehend how any physician can cope with some 200 sulfa drugs, alone or in combination, or with 270 different antihistamines, or perhaps 100 major and minor tranquilizers.

Would-be reformers of medicine and the pharmaceutical industry have continued to decry the proliferation of me-too research [6, 7]. Most recently, Health Action International (HAI), the umbrella organization for most third world health and consumer advocacy groups, has forced the issue into the international arena. One of their chief concerns is the proliferation of dangerous and noninnovative drug products on the international market [8–11]. HAI contends that profit incentives motivate the multinational pharmaceutical industry to spend too much time, effort, and money on me-too research, as well as on research directed towards finding new "follow-on" uses for already marketed drugs. These critics state that while such research yields great profits for the industry, it ignores the therapeutic needs of developing nations, and they advocate the adoption of such concepts as restricted drug lists, formularies, and other means of limiting the types and numbers of drugs available for global consumption [11].

Pharmaceutical firms and other industry proponents claim, however, that few of the major pharmaceutical advances of the past 50 years would have been possible were it not for me-too and follow-on research [12, 13]. Industry supporters hold that "molecular modification is the essence of effective pharmacology" and that without it, most original advances would be unavailable [13]. In addition, these proponents hold that newer drug products often offer significant therapeutic and economic advantages over originator drugs, including increased efficacy, patient compliance, and safety, as well as decreased total treatment cost [12, 13].

Yet, despite contrary opinion, industry critics continue to contend that me-too and follow-on research is trivial, insignificant, and inconsequential to the overall goal of improved health care. In order to investigate the validity of these contentions, we have examined the World Health Organization (WHO) Model List of Essential Drugs for the inclusion of molecularly modified drugs, as well as drugs listed for therapeutic indications discovered subsequent to the originally approved uses. We chose this document as the basis for our analysis because of its global acceptance as a standard of essential therapy.

The Birth of the Essential Drug Concept

In a report to the Twenty-eigth World Health Assembly in 1975, the WHO addressed the concern of rational drug use in developing nations [14]. It was at this meeting, after reviewing the successful implementation of basic drug schemes by several countries, that the idea of an essential drug list was born. In 1977, after considerable consultation with experts in public health, medicine, pharmacy, and drug management, the Expert Committee on the Selection of Essential Drugs proposed an initial list. This document contained those drugs deemed by the WHO to be essential and necessary to address minimally the health and medical needs of any developing nation. The essential drug list recommends the formulations, administration regimens, and therapeutic indications for each drug.

The WHO also established criteria for selecting essential drugs [15, 16]. An important criterion is that selected drugs be available within a country at all times in adequate amounts and in appropriate dosage forms. Additional selection criteria, based on local circumstances, include the epidemiology of prevalent diseases and conditions, the availability and location of treatment facilities, the expertise of health personnel, financial resources, and genetic, demographic, and environmental factors. All essential drugs must be proven safe and effective in clinical use and have adequate and documented stability and bioavailability data. When more than one drug is available to treat the same indication, the drug and formulation chosen should possess the best benefit/risk ratio. In determining this ratio, policymakers must consider efficacy, safety, quality, total treatment cost, and availability.

The essential drug list is revised when the Expert Committee feels that "definite advantages are considered to accrue" to the therapeutics of the indication(s) in question [16]. The Expert Committee reviews and updates the list approximately every 2 years to account for changes in global health priorities, as well as progress made in pharmaceutical research. This list is intended to serve as a universal model, which each developing country adapts to its particular medical and drug needs. The list is not to be considered the definitive tool in framing national formularies; rather, it is meant to help developing nations identify a "common core" of basic drug needs [15]. Much of the opposition and controversy surrounding the essential drug list, however, is concerned with its potential use as the basis for restricted drug lists, formularies, or as a policy for reimbursement purposes [12, 17].

METHODS

We reviewed all substances listed in each of the five versions of the WHO Model List of Essential Drugs [15, 16, 18–20]. Because we were interested in drug entities, we omitted all devices, blood substitutes, immunologicals and vaccines, vitamins and minerals, diagnostic agents, solutions used to correct fluid and electrolyte disturbances, fixed combination products, and oxygen. Through the use of these selection criteria, less than 30% of all drugs listed in each essential drug list were dropped from analysis: in 1987, 26.7% of all drugs were excluded from analysis.

The remaining drugs represent 21 major therapeutic categories listed by the WHO in its essential drug lists. The WHO further broke down these categories into specific subcategories. For example, the therapeutic category, cardiovascular drugs, is comprised of five subcategories: antianginal drugs, antidysrhythmic drugs, antihypertensive drugs, cardiac glycosides, and drugs used in shock or anaphylaxis. For analysis, we retained the major therapeutic categories, using the subcategories to ascertain the therapeutic indications advocated by the WHO for the listed drugs.

We used several sources[1] to trace the international clinical and regulatory histories of each of the remaining drugs in all versions of the essential drug list. Because it represents the most current list, we emphasized the 1987 version in our analysis.

We then determined whether: 1) the drug was a molecular modification of an already existing compound, and 2) whether each drug's listed indications were follow-on indications subsequent to the originally approved indication(s).

For the purposes of this study, a me-too drug was defined as a substance in the same chemical class and used for the same therapeutic indication as the innovator drug. Me-too drugs were counted once per therapeutic category, although, in some instances, a single drug was listed more than once within a therapeutic category because it was listed under multiple subcategories. Drugs listed in more than one therapeutic category and that were me-too drugs in each category were counted once for each applicable category. For example, codeine was counted as a me-too in the analgesia category, as an antidiarrheal in the gastrointestinal category, and as an antitussive in the respiratory tract category.

A drug with indications approved subsequent to the first approved indication(s) was considered a follow-on drug.[2] As with me-toos, drugs with follow-on indications were counted once per therapeutic category. An example of a drug with multiple follow-on indications is propranolol, originally indicated for use in cardiac arrhythmias and subsequently approved for angina, hypertension, and migraine headache.

We assigned me-too and follow-on status for each drug and its indication(s) listed in all versions of the essential drug list. We examined the drugs included on the five essential drug lists by tabulating the number of total drugs, total indications, and the indications per drug for each list. We then determined the proportion of me-too drugs to all analyzed drugs by essential drug list version and by the WHO designated therapeutic category. A similar analysis was performed for the inclusion of drugs with follow-on indications.

RESULTS

The net number of essential drugs has grown with each essential drug list revision (Table 1). The total number of drugs listed in 1977 was 208; by 1987, the number was 266, an increase of 27.9%. The number of drugs meeting our requirements for

[1] The sources used are: *The United States Dispensatory and Physician's Pharmacology*, 26th ed., 1967; Goodman and Gilman's *The Pharmacologic Basis of Therapeutics*, 7th ed., 1985; Paul de Haen's *Nonproprietary Name Index*, Vol. XII, 1980; Paul de Haen's *Nonproprietary Name Index*, Vol. XVII, 1986.

[2] Through the use of the sources noted above, the follow-on status was determined using international approval dates. In a few cases, primarily for those drugs used prior to 1950, international approval dates could not be reliably obtained. Follow-on status for the indications of these drugs was determined based on widely accepted international clinical usage.

Table 1 Trends of Drugs on the Essential Drug Lists

Year	Total Drugs	Analyzed Drugs[a]	Analyzed Indications[a]	Indications per Drug
1977	208	159	171	1.075
1979	243	171	188	1.099
1983	250	178	201	1.129
1985	254	187	214	1.144
1987	266	195	236	1.210

[a] Drugs and indications meeting criteria for study inclusion.

analysis also increased, from 159 drugs representing 171 indications in 1977, to 195 drugs with 236 indications 10 years later. The indications per drug also rose steadily over the 10-year period.

Me-too Analysis. Overall, nearly one-half (48.7%) of all drugs analyzed in the 1987 essential drug list are me-too drugs. While the absolute number of me-too drugs has risen steadily, it has been accompanied by increases in the number of total new drugs added (Table 2). Thus, the proportion of me-too drugs to total drugs has remained fairly constant.

In 1987, a total of 21 new drugs was added to the essential drug list; of these, 17 met the criteria established for inclusion in our analysis. Twelve (57.1%) of the analyzed drugs represent molecularly modified compounds. The majority (64.7%) of these new me-too drugs are antiinfective agents, with six indicated for use against tropical diseases such as malaria and trypanosomiasis.

Figure 1 illustrates me-too drugs as a percentage of total drugs listed in 12 selected therapeutic categories. The therapeutic categories included in Figure 1 represent those categories with either a sufficient total number of drugs or adequate percentages of me-too drugs to warrant graphic presentation. Drugs in these categories represent nearly 94% of all analyzed drugs. Eight therapeutic categories included 50% or more me-too drugs: analgesics, antiinfectives, cardiovasculars, diuretics, hormones, ophthalmologics, psychotherapeutic agents, and respiratory tract drugs. The hormone category has the greatest proportion of me-too drugs, due most likely to the fine-tuning required of the original adrenal corticosteroids and contraceptive hormones in order to lessen their side effects.

Of interest is the fact that neither the beta-blockers nor cephalosporins, two drug classes traditionally maligned for their me-too spin-offs, are included as me-too drugs; indeed, cephalosporins are not even listed as essential drugs.

Table 2 Analysis of Me-too Drugs on the Essential Drug List

Year	Analyzed Drugs[a]	Number of Me-too Drugs	Percentage of Me-too Drugs
1977	159	75	47.2
1979	171	78	45.6
1983	178	82	46.1
1985	187	83	44.4
1987	195	95	48.7

[a] Drugs and indications meeting criteria for inclusion.

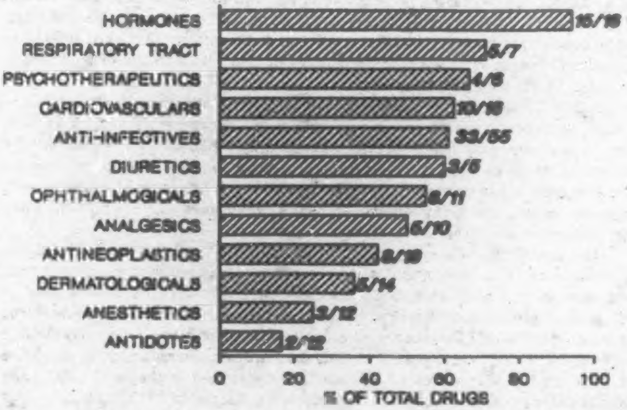

Figure 1. Me-too drugs as percentage of total drugs for selected therapeutic categories.

Often, a number of listed me-too drugs within a therapeutic category are derived from the same innovator drug. For example, two of the diuretics, hydrochlorothiazide and furosemide, are derived from chlorothiazide, and six penicillin derivatives arise from the original benzylpenicillin, Penicillin G.

Follow-on Indications Analysis. A total of 46 drugs (23.6%), representing 58 indications, were listed in the 1987 essential drug list for therapeutic uses approved subsequent to the initially approved indication(s) (Table 3). Of these drugs, 19 (41.3%) are also listed for their originally approved indications. The number of drugs with follow-on indications included in the essential drug lists has steadily increased for each revision, with the largest jump seen in the 1987 version.

Unlike the situation noted with the me-too drugs, in 1987 only one new drug, dl-Methionine, first used as a nutritional supplement, was listed with a follow-on indication for use as an antidote. Six previously listed drugs, however, were listed for new therapeutic indications. It is these new indications for already listed drugs that count for the increasing presence of drugs with follow-on indications on the WHO essential drug list. This fact is most dramatically evident in the 1987 list, where nearly one-quarter (24.6%) of all listed indications (236) are follow-on indications. In that same list, the percentage of drugs with follow-on indications increased 17.9% from the 1985 list.

Table 3 Analysis of Drugs on the Essential Drug List with Follow-on Indications

Year	Analyzed Drugs*	Analyzed Indications*	Follow-on Drugs (%)	Follow-on Indications (%)
1977	159	171	30 (18.9)	32 (18.7)
1979	171	188	35 (20.5)	37 (19.7)
1983	178	201	37 (20.7)	42 (20.9)
1985	187	214	39 (20.9)	48 (22.4)
1987	195	236	46 (23.6)	58 (24.6)

* Drugs and indications meeting criteria for study inclusion.

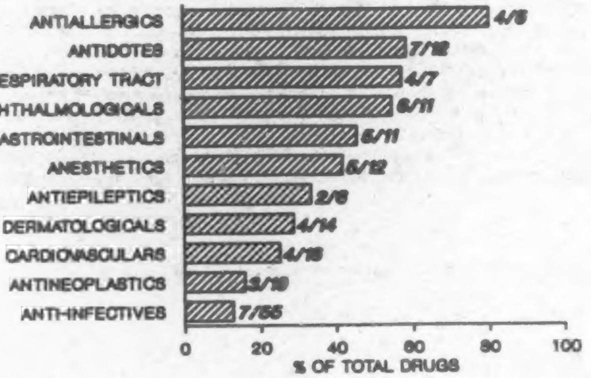

Figure 2. Drugs with follow-on indications as percentage of total drugs for selected therapeutic categories.

Figure 2 illustrates the percentages of drugs with follow-on indications in 11 selected therapeutic categories. These categories, representing 86% of all analyzed drugs, were graphically depicted because they had either a sufficient total number of drugs or adequate percentages of drugs with follow-on indications. Five therapeutic categories are notable for their high proportions of drugs with follow-on indications: antiallergics, antidotes, gastrointestinals, ophthalmologicals, and respiratory tract drugs.

The antiallergics category has the greatest percentage of drugs with follow-on indications. The four drugs in this category—dexamethasone, epinephrine, prednisolone, and hydrocortisone—are hormones whose predecessors were all first used in adrenal insufficiency. In particular, hydrocortisone and epinephrine are each listed in 1987 for three separate follow-on indications. Of note is the fact that both have long been a part of the standard drug armamentarium; epinephrine was first used as a vasopressor and adrenal supplement in the early 1900s, and hydrocortisone was originally used in Addison's disease in 1952.

DISCUSSION

Because our definition of me-too drugs is based on similarities in chemical structure, rather than the physiologic effect or mechanism of action, determination of a drug's me-too status is conservative. For example, indomethacin, an indole compound, and ibuprofen, a propionic acid derivative, are both considered nonsteroidal antiinflammatory agents. They both have analgesic properties made possible through their inhibitory actions on prostaglandin biosynthesis and, with a less conservative definition, could be considered me-too drugs of the analgesic progenitor, salicylic acid. We did not consider indomethacin and ibuprofen to be me-toos of salicylic acid, however, because of their distinctly different chemical structures.

We also did not include as me-toos those drug categories derived from an innovator drug that was originally a member of a different therapeutic class. For example, we did not consider the thiazide diuretics to be me-too derivatives of the sulfonamide antibiotics, although thiazide diuretics were discovered as an offshoot of sulfonamide side-effect research. Given that it is discoveries of entirely new therapeutic classes that often constitute medical breakthroughs, our analysis thus underestimates true me-too research and development.

Medical history is replete with examples of new therapeutic classes that have arisen from methodical tinkering with already-existing compounds. Figure 3 illustrates this concept as it applies to the 1987 essential drug list. Four important therapeutic classes of drugs included on that list—sulfonamide antibiotics, diuretics, uricosurics, and oral antidiabetic agents—are ultimately derived from the drug prontosil, discovered by Domagk more than 50 years ago. Underlined in this figure are those drugs currently listed in the 1987 essential drug list. Other, less dramatic examples exist in the essential drug lists. Molecular changes in mercaptopurine, a chemotherapeutic agent, led to allopurinol, a xanthine oxidase inhibitor used to treat gout, and azathioprine, an immunosuppressant. Cocaine, an analgesic, eventually gave rise to the cardiovascular and anesthetic drugs procainamide, lidocaine, bupivicaine, and tetracaine. Research on norepinephrine's chemical structure led to alpha-methyldopa, an antihypertensive. Phenytoin, a congener of the barbiturates originally used as sedatives, proved useful in treating epilepsy. Finally, another barbituate congener, thiopental, is widely used in general anesthesia.

To analyze the contributions made by me-too and follow-on research, we chose the WHO essential drug list because it represents, on an international level, a pared-down model of the most basic drugs needed to alleviate the health and medical problems facing developing nations. Much of the current criticism aimed at the pharmaceutical industry regarding me-too and follow-on research comes from the international arena. The WHO essential drug list, however, is not the only vehicle for analysis. Other possibilities for further research include state Medicaid formularies, Health Maintenance and Preferred Provider Organization formularies, and national formularies, such as those used in Sweden and the United Kingdom.

Finally, while we present a quantitative picture of me-too and follow-on research, we have not tried to judge whether the inclusion of such drugs and indications represents an improvement over the innovator drugs. Nor have we examined the omission of drugs often regarded as the "gold standards" in most Western countries. We address this problem indirectly, however, by illustrating the importance of me-too research, as well as citing specific examples. Other investigators have also examined the therapeutic improvements made possible by me-too and follow-on research [13, 21–23].

CONCLUSION

Third world health advocacy groups, led primarily by Health Action International, have been prominent voices attacking the pharmaceutical industry's research motives and actions. We refute the contention that the industry's research leads only to useless and redundant drugs that harm less affluent nations. Our study demonstrates that me-too and follow-on research play a vital role in producing drugs that benefit underdeveloped countries. Nearly one-half of the drugs present on the WHO essential drug list are available as a result of me-too research, and nearly one-quarter of the therapeutic indications described by the WHO essential drug list are treated by drugs originally indicated to treat some other disease or condition.

The global acceptance of the essential drug list testifies to its medical and public health significance. As of 1987, more than 100 developing countries have prepared essential drug lists, another 24 are presently in the planning stages of essential drug list adoption, and another 19 nations are seriously considering the concept [24]. If, as promoted by the WHO, the essential drug list in fact is composed of drugs that are truly essential, then our findings illustrate the importance of me-too and follow-on research.

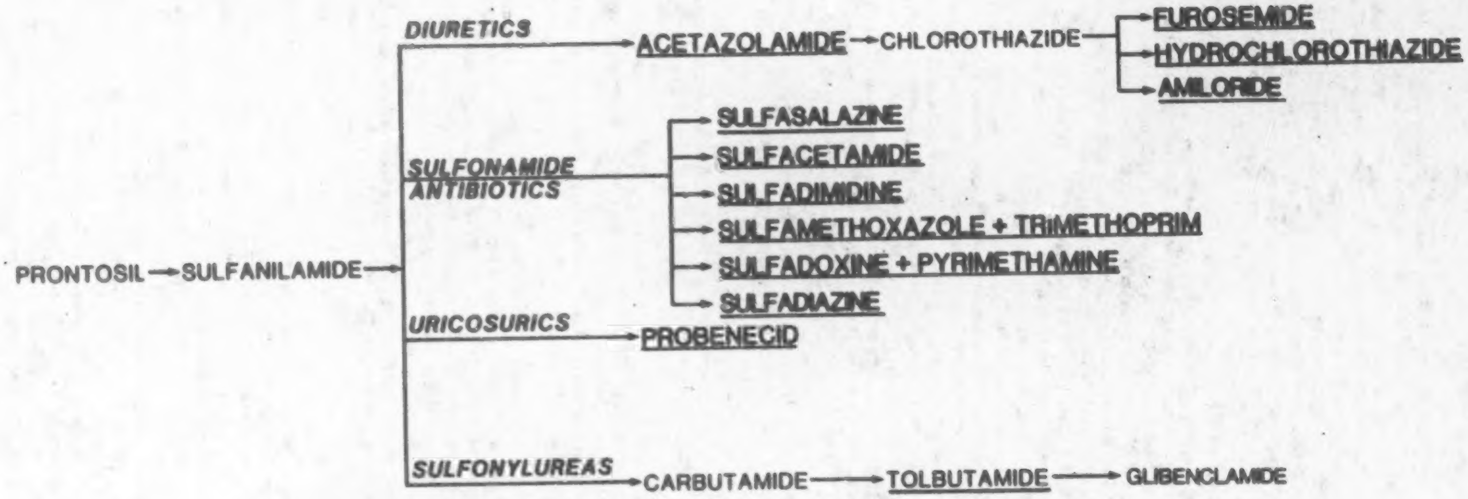
PRONTOSIL
SULFANILAMIDE
DIURETICS
ACETAZOLAMIDE
CHLOROTHIAZIDE
FUROSEMIDE
HYDROCHLOROTHIAZIDE
AMILORIDE
SULFONAMIDE ANTIBIOTICS
SULFASALAZINE
SULFACETAMIDE
SULFADIMIDINE
SULFAMETHOXAZOLE + TRIMETHOPRIM
SULFADOXINE + PYRIMETHAMINE
SULFADIAZINE
URICOSURICS
PROBENECID
SULFONYLUREAS
CARBUTAMIDE
TOLBUTAMIDE
GLIBENCLAMIDE

Figure 3. Example of how me-too research within a therapeutic drug class results in the discovery of other therapeutic classes and indications. Drugs underlined are those drugs included on the 1987 WHO essential drug list.

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AMERICA'S PHARMACEUTICAL RESEARCH COMPANIES

A COST-EFFECTIVE SOURCE OF IMPORTANT NEW MEDICINES

November 15, 1989

Pharmaceutical
Manufacturers
Association

AMERICA'S PHARMACEUTICAL RESEARCH COMPANIES -- A COST-EFFECTIVE SOURCE OF IMPORTANT NEW MEDICINES

EXECUTIVE SUMMARY

Contrary to the recent "findings" of the staff of the Senate Special Committee on Aging, the research and development undertaken by prescription drug manufacturers produces significant new compounds that improve existing therapies and drive down the overall cost of medical care. The staff's July 18, 1989 briefing paper, entitled Prescription Drug Prices: Are We Getting Our Money's Worth?, contains fundamental errors of data interpretation that lead to erroneous conclusions.

The U.S. leads in the discovery of "world class" drugs. Nearly half of the new medicines that achieved worldwide acceptance between 1975 and 1986 originated in the United States. And over 80% of the most prescribed drugs in the United States were patented by private companies. These include dozens of breakthrough medicines for common and rare diseases. In the last decade, private companies have developed and received marketing approval for pioneering drugs that dissolve gallstones, lower blood pressure and cholesterol, break up blood clots, prevent anemia, fight cancer, and prolong the lives of AIDS victims. The industry's research investment grows every year. The portion of sales revenues reinvested into R&D by pharmaceutical research companies surged by 43% in the last 10 years, topping 16% of

sales in 1988, the highest for any established U.S. industry. This year, PMA member companies will spend $7.3 billion on R&D, exceeding total funding for biomedical research by the National Institutes of Health. Indeed, the unparalleled success of these efforts has enabled striking improvements in patient care; and it has allowed the U.S. industry to maintain a positive trade balance in the face of heightened competition from abroad.

Unfortunately, these achievements and expenditures of resources are not reflected in the staff's briefing paper. Instead, the staff misconstrued available data in ways that lead it to the erroneous conclusion that the "bulk of the research and development by prescription drug manufacturers produces insignificant new compounds that add little or nothing to drug therapies already marketed." The opposite is true.

There are five fundamental flaws in the staff's analysis:

- o An Inappropriate Measure of Pharmaceutical Innovation was Used in the Analysis: New Molecular Entities (NMEs) reflect the industry's contribution to the development of innovative new therapies and account for approximately 80% of all industry research expenditures. In fact, nearly half (47%) of the 182 NMEs were considered by the Food and Drug Administration to represent a significant or moderate therapeutic gain. The staff greatly diluted these achievements by also counting as "new drugs" hundreds of minor improvements to existing products (e.g., chemical derivatives, new formulations, IV bags, and even generic drugs).

- o The Cost of Research and Development was Improperly Applied to all New Products: Between 1981 and 1988, PMA member firms spent approximately $26.2 billion on the development of NMEs and $6.5 billion on improvements to existing products. By incorrectly assuming that an average of $125 million is spent to develop each new product rather than only NMEs, the committee staff overestimated the sums spent to develop "C" rated drugs, concluding that "as much as $37 billion" was spent. Studies by noted economists have indeed concluded that developing an NME costs over $125 million on average. Modifications to existing products obviously cost far less.

- The FDA Drug Rating System is Not a Fair Measure of Pharmaceutical Innovation: FDA's rating system does not measure the ultimate or even current value of medicines on the market. Designed only to serve as an FDA administrative tool to allocate reviewing resources, the rating does not take into account that a drug's actual value to patient care evolves with widespread use. Such experience often reveals new uses, or added value to physicians who need a broad selection of drugs in order to accommodate variation in patient response to medications.

- The Top 25 Firms were Improperly Chosen and Do Not Represent the Performance of Major Pharmaceutical Companies: The top 25 companies -- ranked according to prescription drug sales -- accounted for 61% of all "A" rated drugs and [illegible]% of all NMEs approved between 1981 and 1988. The Committee staff incorrectly used a ranking of firms based on sales that also included nutritional and over-the-counter products. Using this different group of firms, the staff concluded that the major firms developed only 39% of the "A" rated or "important" new drugs between 1981 and 1988.

- The Pharmaceutical R&D Process is Lengthy and a High Risk Enterprise: Drug development generally spans 7-10 years from discovery to FDA approval. Only 1 out of 5 products tested in the clinic makes it to market. Many products are developed in parallel by different firms, and incremental discoveries during this process can lead to important therapeutic advances. In fact, a recent study of the World Health Organization's Essential Drugs List concludes that nearly 50% of the

> drugs recommended by the WHO are not the pioneer drugs of their respective classes.[3] For example, two of the recommended diuretics, hydrochlorothiazide and furosemide, are derived from chlorothiazide, and six penicillin derivatives arise from the original benzylpenicillin, Penicillin G. Following the Committee staff's reasoning, one might conclude that these essential medicines are "me-too" drugs of little therapeutic gain.

Considering the conclusions the staff reached from the data available, it is obvious that it fundamentally misunderstands the nature of pharmaceutical research and development and the high risks involved in the new drug discovery process. If analyzed objectively, the data contained in the staff briefing paper clearly shows that the U.S. pharmaceutical industry is successfully developing new products that represent therapeutic advances, both by FDA's standards and by current standards of physician care. We urge the Committee to consider the data itself, rather that adopt the staff's opinions about the data.

INTRODUCTION

The report prepared by the staff of the Senate Special Committee on Aging, Prescription Drug Prices: Are We Getting Our Money's Worth? (July 18, 1989) ("staff report") attempts to examine the pharmaceutical industry's performance in discovering and developing innovative new therapies. The pharmaceutical industry invests billions of dollars a year in its efforts to develop new and useful products; this year alone, PMA member firms will spend over $7 billion in private funds on research and development. This investment has led to several successes, most notably that of the 50 most prescribed drugs in the United States, private industry was the source of 84% of these new drugs. Accordingly, the pharmaceutical industry welcomes all reasoned efforts to measure the efficacy of its research expenditures.

The staff report, however, suffers from several fundamental flaws that cause it to present a distorted perspective on the value of recent pharmaceutical research. Indeed, rather than describing an industry that is a world-leader in product innovation and that is one of the most research intensive industries in the United States, the staff report paints a picture of an industry that has lost its creative edge and that spends its resources mimicking each others' products. A careful reading of the staff report reveals several fundamental errors in assumptions and analyses that have caused the staff to reach unwarranted conclusions.

The analysis of pharmaceutical innovation and performance is based on a therapeutic rating system used internally within FDA. This system was neither designed to reflect industry's research performance nor to reflect a drug's ultimate medical contribution to patient care, a value that evolves with widespread clinical experience. In addition, a careful analysis of the data, founded in a more thorough understanding of the research and regulatory process, reveals that the staff's conclusions present a biased description of the extent to which the pharmaceutical industry contributes to innovations in health care.

I. AN INAPPROPRIATE ANALYSIS OF 1981-1988 DRUG APPROVALS HAS RESULTED IN FLAWED CONCLUSIONS

A. All New Drug Products v. New Molecular Entities

FDA's classification system involves rating a drug based upon its therapeutic potential as well as its chemical type. The system distinguishes between those drug products that are new molecular entities and those that are derivatives of already marketed products. Between 1981 and 1988, six different chemical types of drugs were approved that account for the 781[1] "drug approvals":

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[1] According to FDA's records, a total of 781 "new drug products" were approved between 1981 and 1988, rather than the 776 analyzed in the Staff report. Other minor inconsistencies in the exact numbers presented in Appendix A of the Staff report were also discovered, but do not warrant discussion.

Type 1	New Molecular Entity: The active moiety has not been previously marketed in the U.S.
Type 2	New Salt: The active moiety is marketed in the U.S. by the same or another manufacturer, but the particular salt, ester, or derivative is not yet marketed in the U.S.
Type 3	New Formulation: The compound is marketed in the U.S. by the same or another manufacturer, but the particular dosage form or formulation is not.
Type 4	New Combination: The product contains two or more compounds which have not previously been marketed together in a drug product in the U.S. by any manufacturer.
Type 5	Already Marketed Drug Product: The product duplicates a drug product already marketed in the U.S. by another firm.
Type 6	Already Marketed Drug Product by the Same Firm: The product adds a new indication for a drug product already marketed in the U.S. by the same firm.

Innovation in the pharmaceutical industry is defined by efforts to discover new therapeutic agents to treat diseases not currently treatable or in a more effective manner. Such advances may appear modest, but be clinically significant to patients, or they may be dramatic breakthroughs based on a single major advance in understanding a particular disease process or how the body's basic biological mechanisms can be influenced.

Although all of the 781 "new drug products" approved between 1981 and 1988 offer some potential for more effective treatment, New Molecular Entities (NMEs) are the true measure of industry's innovative performance. By definition, NMEs are those products representing new chemical structures never previously available in the U.S. to treat a particular disease. The research and development underlying the discovery of a novel NME generally relies upon breakthrough discoveries that demonstrate the industry's commitment to the high risk process of drug discovery. Several studies of pharmaceutical innovation have been published, all of which rely upon the well-considered conclusion that NMEs are the best measures of innovative success.[2]

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[2] See Trends and Changes in Drug Research and Development, edited by Bryan C. Walker and Stuart R. Walker, Kluwer Academic Publishers, Lancaster, UK: 1988; and "The Measurement of Pharmaceutical Innovation," William Wardell and Jean DiRaddo, J. Clin. Pharmacol. 20(1), January 1980.

The staff report contends that "the bulk of research and development by prescription drug manufacturers produces insignificant new compounds that add little or nothing to drug therapies already marketed." However, the staff has improperly focused on all 781 new drug applications approved between 1981 and 1988. Instead, the analysis should focus on the 182 NMEs that account for approximately 80% of all research and development expenditures (PMA Annual Survey Reports, 1981 through 1989). Only about 20% is spent on the other 599 drug products representing chemical derivatives of marketed products, new formulations, new combinations, as well as duplicates of already marketed drugs. These non-NME approvals are new products that, by definition, should be evaluated on a different basis.

PMA conducts an annual survey of sales and research and development activities applicable to ethical pharmaceuticals which represents the authoritative source of data on the industry. In this survey, firms are requested to provide data on how their R&D is allocated to the discovery of new ethical pharmaceuticals. Based upon responses over the 1981-1988 time frame, our data indicate that approximately 80% of R&D is allocated to research on new products and approximately 20% to significant improvements and/or modifications of existing products.

TABLE 1
NEW DRUG APPROVALS BY CHEMICAL TYPE 1981-1988

Chemical Type	Frequency	
New Molecular Entity	182	(23%)
New Salt	12	599 (77%)
New Formulation	203	
New Combination	32	
Already Marketed Product	349	
Already Marketed Product (Same firm)	3	
TOTAL	781	

By focusing solely on the 182 NMEs approved between 1981 and 1988, one can better understand how innovative industry has been because the therapeutic significance of these discoveries is no longer masked by the multitude of non-NME drug approvals. In fact, the data show that 47% of the NMEs approved were considered by FDA to represent a significant or moderate therapeutic gain. This is a dramatic shift in emphasis from the staff's finding that 84% of the 348 new drugs brought to market by the 25 largest U.S. drug manufacturers offer little or no therapeutic advantage over existing drug therapies.

TABLE 2
NEW DRUG APPROVALS BY THERAPEUTIC RATING 1981-1988

Therapeutic Rating	NMEs	
A	23	47%
B	62	
C	97	
TOTAL	182	

B. Non-NME Drug Products

Although NMEs are clearly the true measure of industry's innovative performance, an explanation of the 599 other drugs helps one to understand why these products should not be included in an analysis of innovation.

As described earlier, the non-NME products generally represent modifications to marketed products -- new formulations, new combinations of drugs, new chemical derivatives of the active ingredient, or duplicates of an already marketed product.

New formulations, or line extensions, account for 203 of the 599 drug approvals between 1981 and 1988. Although 175 of these were considered "C" products by FDA, they play an important role in health care delivery. Such modifications frequently address patient preferences, ease of administration, or other factors that influence patient compliance. For example, an oral product may be reformulated for intravenous use to facilitate hospital administration or may be formulated as a suppository to facilitate administration to elderly patients who have difficulty taking oral medications. Significantly, long-acting injectable forms of phenothiazines, for example, have improved chronic treatment of psychotic patients who often fail to take their medicines as prescribed. By limiting non-compliance problems, physicians can frequently avoid institutionalization (Wardell and DiRaddo, J. Clin. Pharmacol. Vol. 20, No. 1, January 1980).

Thirty-two products approved between 1981 and 1988 were new combinations of already marketed products. Although 28 of these products were considered "C" drugs, this category represents an effort on the part of the pharmaceutical industry to facilitate and improve drug therapy. Often patients take multiple medications, some of which are frequently prescribed simultaneously. Beta blockers and diuretics are a good example of such a combination. By formulating two drugs into a single product, compliance is improved and confusion reduced for patients on complicated therapeutic regimens.

The largest category of non-NME approvals (349) represent duplicates of already marketed drugs, including generics. Before 1985 when the Drug Price Competition and Patent Term Restoration Act of 1984 went into effect and an alternative approval process was implemented, firms interested in marketing generic versions of brand-name products were required to submit a new drug application which was rated "5C" by FDA. These products, by definition, are not a measure of the industry's innovative performance.

The "duplicate product" category also includes 168 (48%) Large Volume Parenterals (LVPs) or products that are primarily solutions administered in the hospital through intravenous administration kits. LVPs, although an essential part of inpatient hospital care, represent an insignificant percentage of the total amount spent on research and development by the pharmaceutical industry. In 1987, less than 0.2% of all R&D expenditures were committed to the development of large volume parenteral products (PMA Annual Survey Report, 1987-1989).

Further, LVPs are largely considered a commodity market in which a manufacturer, in order to capture a hospital market, must offer a full line of products. Each of these products necessitates a separate New Drug Application, even if it merely represents a different percentage of a dextrose solution. In the 1980's, many of the "new" LVP products approved by FDA represented changes made to the plastic containers for these solutions, not to the solutions themselves. Because any solution in a plastic container is considered a drug, when the industry introduced new generation plastics that eliminate the use of polyvinyl chloride or that exhibit improved moisture/gas barrier properties, each product whose container was modified required a new drug application. FDA classified such products as "C" drugs.

By analyzing the 599 non-NME drug products, one quickly realizes the impropriety of including these products in an analysis of pharmaceutical industry innovation. Although a large number of these products were considered "C" drugs, modifications that affect performance or patient compliance represent significant improvements to the delivery of medical care. Further, by not recognizing that this category includes generic drugs and LVPs due to regulatory requirements, the staff has dramatically masked industry's contribution to pharmaceutical innovation and improved health care.

C. Cost of Research and Development

The Committee staff concluded that the industry has been spending many billions of dollars on research and development for new drugs offering little therapeutic value. This conclusion, however, resulted from an inappropriate application of PMA's study which concludes that it costs $125 million to develop a New Molecular Entity. By assuming that the R&D cost for every approved product, NME and non-NME, is $125 million, the staff calculated that the top 25 U.S. drug makers spent $37 billion on R&D to produce 292 "C" drugs.[3]

A more accurate reflection of R&D expenditures dedicated to new drug development may be calculated from PMA's Annual Survey of worldwide R&D expenditures. From 1981 to 1988, a total of $32.7 billion was spent by PMA member companies on worldwide research and development.

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[3] The Staff has not only inappropriately applied the estimate from PMA's study to non-NME drug products, but has also not recognized that the average of $125 million includes the cost of pursuing "dry holes" as well as opportunity costs, i.e., revenues foregone by investing in research and development rather than in opportunities with more immediate returns.

Based on our data that approximately 80% of R&D expenditures during this time period was devoted to the development of NMEs, a more accurate estimate is that $26.2 billion was dedicated to the advancement of scientific knowledge and the development of novel products, while only $6.5 billion was spent on research oriented to significant improvements or modifications of existing products.

However, it is inappropriate to view these R&D expenditures as directly related to the development of the drugs approved between 1981 and 1988. Because the drug development process spans seven to ten years, current research is targeted at developing future therapies to meet current and anticipated medical needs. In order to ensure a healthy and internationally competitive industry, U.S. pharmaceutical firms must be able to maintain state-of-the-art research programs. Current sales are, from a practical standpoint, funding research programs designed to develop drugs to treat many of the significant unsolved medical problems that still face Americans.

TABLE 3
R&D SPENDING BY PMA MEMBER FIRMS

Year	Worldwide Expenditures
1981	$2.3 Billion
1982	2.8
1983	3.2
1984	3.6
1985	4.1
1986	4.7
1987	5.5
*1988	6.5
TOTAL	$32.7 Billion

* Estimated figure

D. 25 Largest U.S. Drug Manufacturers

The staff also focused heavily on an analysis of products made by the "top twenty-five manufacturers (by sales) in the United States." It appears that these 25 firms were chosen based upon a listing that separately identified subsidiaries of the parent corporation and that included U.S. sales for not only prescription drugs, but also nutritional and over-the-counter products. Neither nutritional nor OTC products are germane to the staff's attempt to assess the industry's success in bringing innovative new therapies to market.

PMA's Annual Survey, which measures U.S. sales for ethical pharmaceuticals[4] only and which takes into account corporate structure, identifies a different group of firms that we believe more accurately reflects the contributions of major drug manufacturers dedicated to the development of significant new prescription pharmaceuticals.[5]

The staff report claims that the top 25 companies accounted for only 44% of all new drugs and only 39% of the "A" rated drugs. When the data are analyzed using PMA's redefinition of the top 25 companies, a distinct shift in emphasis is observed. Rather than accounting for only 39% of all "A" rated drugs, our analysis demonstrates that the major firms were responsible for 61% of these important therapeutic advances. When the success of these firms in developing innovative new therapies is measured, the data are even more revealing. Statistics show that the major firms are responsible for 69% of the NMEs approved between 1981 and 1988. In fact, the top 25 firms accounted for 62% of the 85 NMEs considered significant or moderate therapeutic advances.

TABLE 4
NEW DRUGS INTRODUCED BY 25 LARGEST FIRMS

	Committee staff Top 25 Co.	PMA Top 25 Co.	PMA All Members	All Co.
NMEs				
1A	7 (30%)	11 (48%)	18 (78%)	23
1B	30 (48%)	42 (68%)	52 (84%)	62
1C	58 (60%)	73 (75%)	91 (94%)	97
Total	95 (52%)	126 (69%)	161 (88%)	182
All New Drugs				
A	12 (39%)	19 (61%)	26 (84%)	31
B	43 (46%)	58 (62%)	78 (84%)	93
C	291 (44%)	362 (55%)	463 (70%)	657
Total	346 (44%)	439 (56%)	567 (72%)	781

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[4] Ethical pharmaceuticals are products, including biological and medicinal chemicals, used for the cure, alleviation, mitigation, treatment, prevention or diagnosis of disease in humans or animals and promoted primarily to the medical, pharmacy and allied professions; includes products for over-the-counter ethical sales (i.e., promoted to the professions, not products on display for purchase by consumers) as well as for ultimate dispensing by prescription only. (PMA Annual Survey, 1987-1989)

[5] Based upon 1987 U.S. sales, the top 25 companies should include: Abbott, American Home, Beecham, Boehringer Ingelheim, Bristol-Myers, Burroughs Wellcome, Ciba-Geigy, Glaxo, Hoffmann La-Roche, ICI, Johnson & Johnson, Lederle (American Cyanamid), Eli Lilly, Marion, Merck, Merrell Dow (Dow), Pfizer, Rorer, Sandoz, Schering, Smith Kline and French, Squibb, Syntex, Upjohn, and Warner Lambert. This ranking of the top 25 firms was not modified to reflect recent mergers.

Thus, by analyzing the drug approvals using a list of companies rated by sales that includes nutritional and OTC products while also failing to recognize corporate structure, the staff has presented a biased description of the extent to which large firms contribute to innovation in the prescription-based pharmaceutical industry. Further, by not focusing on the true measures of pharmaceutical innovation -- NMEs -- the staff has painted a biased picture of the industry's success in bringing innovative new therapies to market.

II. FDA CLASSIFICATION SYSTEM AS THE BASIS FOR AN ASSESSMENT OF PHARMACEUTICAL INNOVATION

As demonstrated by a careful analysis of the data on drug approvals between 1981 and 1988, a different picture of the pharmaceutical industry's performance is painted than that presented in the staff report. However, to comprehend fully the fallacy of the staff's conclusions, it is important to consider both the intent of FDA's drug rating system and how that system is influenced by the nature of drug research and development. The Committee staff incorrectly assumed that the rating system is a fair measure of pharmaceutical innovation.

A. Intent of FDA System and What It Represents

In an effort to accord the highest priority for review to drugs deemed to have the greatest potential for contributing to improved medical care, FDA instituted, in 1979, an IND/NDA classification system. That system is intended to provide a convenient administrative mechanism for categorizing drug applications based upon the drug's chemical type and therapeutic potential. The stated objective of the system is: "For those New Drug Applications (NDAs) received after October 1, 1978, [to] decrease the total FDA processing time for approval of those judged to be promising therapeutic advances, while also decreasing to a lesser extent approval time for other new drug applications." (New Drug Evaluation Project Briefing Book, FDA, March 1981). Those products deemed to be a major ("A") or modest ("B") therapeutic gain are to receive expedited action.

The rating system is intended to provide a "convenient way of describing drug applications upon initial receipt and throughout the review process" (FDA Staff Manual Guide BD4820.3, Feb. 19, 1982) in order to provide FDA with an internal system for prioritizing activities. Because the clinical significance of a product may not be obvious immediately, some drugs that may have appeared to be "C" drugs during review may ultimately prove to have greater or unexpected therapeutic importance after widespread use. Despite such a finding, the therapeutic rating of the drug does not change following FDA approval. Indeed, as an internal FDA administrative tool, one would not expect the rating to change. Thus, the classification, finalized at approval, does not necessarily reflect a drug's current, or ultimate, contribution to patient care based upon long-term clinical experience.

In fact, some of the more important advances in medical therapy have occurred during the post-marketing phase, while observing patients taking a drug for an entirely different indication. Drs. William Wardell and Lorraine Sheck highlighted examples of such discoveries, noting that some of the more important therapeutic advances of the past three decades were discovered in this manner:

> . . . all the main classes of psychotropic drugs (the major tranquilizers and both types of antidepressants); the thiazide diuretics for diabetes insipidus; the anti-parkinsonian action of amantadine; the anti-inflammatory action of steroids and of phenylbutazone; the anti-gout action of allopurinol; the anti-arrhythmic actions of phenytoin and lidocaine; the uricosuric action of probenecid; acetazolamide for glaucoma and epilepsy; diazepam for status epilepticus; the protective effects of beta blockers (and the probable protective effects of platelet modulators, including aspirin) against myocardial infarction and coronary death; the use of aspirin and sulfinpyrazone in preventing stroke; and the nonsurgical closure, by indomethacin, of patent ductus arteriosus in premature babies. (Rational Drug Therapy, Vol. 17, No. 1, January 1983)

The FDA itself has conceded that it is conservative in its allocation of "A" classifications. In 1980, Marion Finkel, M.D., then Associate Director for New Drug Evaluation at FDA, wrote in the New England Journal of Medicine, that FDA reserves the "A" rating for "drugs that represent truly major advances from the therapeutic standpoint . . . Because of our conservative definition, the rating of 1B has been applied to some drugs that other physicians might designate as 1A." Dr. Finkel further emphasizes that:

> Because the final ratings are made at the time of approval and are often based on relatively limited data, and sometimes on narrowly defined indications for use, it is certainly possible that with more widespread use, a drug would be found to be much more valuable (or, conversely, less valuable) than had been supposed. A rating of 1C (little or no therapeutic gain) does not mean that a drug does not possess certain advantages over other drugs. There are always patients who fail to respond adequately to older drugs or cannot tolerate them and will obtain benefit from a 1C drug; again, certain advantages may emerge after widespread use of a drug that were not apparent in the studies performed before marketing . . . The FDA agrees that the final judge of the usefulness of a drug is the practicing physician. (New Eng. J. Med. 302(3):181-183, Jan. 17, 1980)

As noted by Dr. Finkel, physicians are acutely aware of the variation in responsiveness among patients. Certain patients may not respond adequately, or cannot tolerate, certain drugs in a therapeutic class or they may represent a special situation based upon a compromised physiologic state. A broad selection of drugs with diverse characteristics and mechanisms of action gives the clinician the necessary tools to individualize a patient's therapy.

Evidently, the FDA classification does not accurately reflect sound medical evidence generated through long-term clinical use. Further, FDA classifications are based on decisions made by individual reviewers and Division Directors, not on defined criteria in an open and systematic process. As a result, even as an administrative tool, the system is applied inconsistently and does not necessarily accurately reflect a drug's true potential.

The staff report also implies that FDA's classification includes an assessment regarding whether the drug has the potential for large cost reduction, noting that a "C" rating means that "the compound fails to provide significant economic advantages to the patient, compared to already marketed drugs used for the same ailment." This characterization of a "C" drug is not, however, consistent with FDA's own definition and signifies an overreaching interpretation of that definition.

The definition of a modest therapeutic gain ("B" drug) includes the potential for large cost reduction, but does so only by way of example of criteria to be used in the decision-making process. The rating does not imply that cost reduction must be a factor, as other improvements in medical care are also identified, such as elimination of certain adverse effects, less frequent dosing, and greater patient compliance. The staff appears to have concluded, by implication, that a "C" rating therefore fails to provide economic advantages. Such a conclusion is flawed and, indeed, prior to the Drug Price Competition and Patent Term Restoration Act of 1984, generic duplicates of off-patent drugs were classified as "C" drugs -- proof that cost savings have been and can be associated with "C" drugs.

B. How Therapeutic Ratings are Influenced by the Research and Development Process

The drug development process generally spans seven to ten years. It is therefore inevitable that innovative drugs capitalizing upon an advance in medical knowledge are often developed in parallel by several different firms. When this occurs, FDA will often assign all promising products with a high rating of therapeutic significance, but classify only the first drug to be approved in a class as an "A." All other products, by default, receive a "C" classification, without consideration of the possible advantages that they ultimately may offer. The system also does not recognize the importance to prescribing physicians of parallel development of multiple therapies. If, after widespread use, an "A" drug is discovered to cause alarming adverse side effects, it is important for the physician to have alternative therapies available.

By suggesting that the later-approved "C" drugs do not reflect innovative state-of-the-art research, the staff report displays a fundamental misunderstanding of the research and development process and the risks involved. Companies investing hundreds of millions of dollars in developing new substances have no guarantee that they will be first to market. Neither the FDA nor the pharmaceutical industry can a priori determine which avenue of research will be most fruitful. Thus, to suggest that companies that have invested years of effort and millions of dollars in an attempt to bring an innovative product to market are instead trying to mimic a product that may not have been approved or even existed during the development process, represents an unfair exercise in hindsight that displays a fundamental misunderstanding of the R&D process.

Major advances can also result from the cumulative effects of smaller discoveries relating to the biochemical basis for certain diseases or to additional indications not foreseen at the outset. Such advances have been seen in therapies for hypertension, asthma, and cancer. Perhaps one of the most dramatic examples is the finding that beta blockers, originally approved only for the treatment of dysrhythmia and hypertension, can also treat glaucoma, anxiety, thyroid disease, idiopathic hypertrophic subaortic stenosis, prevent migraines, and reduce mortality and the rate of reinfarction in patients who had already suffered a heart attack (Wardell and Sheck, Rational Drug Therapy, Vol. 17, No. 1, January 1983). Despite these important discoveries, only one of the numerous beta blockers approved during 1981 and 1988 was rated as an "A" drug.

Drs. Wardell and DiRaddo, in a study of pharmaceutical innovation, further caution against the intervention into, and misinterpretation of, outcomes from the complex research and development process:

> Since the medical value of a pharmaceutical innovation can only be fully evaluated after it has reached the market, the earlier in the process a compound is dropped the less will be known about its ultimate therapeutic potential. Thus, the full impact of a censoring process such as regulation that deletes products from ultimate evaluation can never be known. The clinical discovery of new uses for marketed drugs -- by either systematic or serendipitous means -- is exquisitely sensitive to a reduction in the number of new compounds appearing on the market. (J. Clin. Pharmacol. Vol. 20, No. 1, January 1980)

In fact, a recent study by the Center for the Study of Drug Development at Tufts University analyzed the World Health Organization's Essential Drug List, a list of products that has been globally accepted as a standard of essential therapy. The authors concluded that almost half of the drugs were "me-too" drugs, or substances in the same chemical class and used for the same therapeutic indication as the original drug in that class. Further, nearly one-quarter of the drugs were listed to treat indications that represent discoveries made subsequent to the first approved indication. Based upon these findings, the authors concluded that "research dedicated to improving efficacy and safety profiles of innovator drugs, as well as discovering new therapeutic uses, is of medical importance to both developed and underdeveloped nations." (Wastila, L., Ulcickas, M., Lasagna, L., J. Clin. Res. Drug Devel. (1989) 3:105-115)

SUMMARY

In order to interpret correctly any analysis of the clinical significance of new drugs approved since 1981, it is important to understand that the therapeutic rating system is an inconsistently applied, vaguely defined, internal FDA administrative system. This classification, finalized at approval, merely reflects an individual's prediction about a drug's potential contribution to improved medical care based upon limited clinical trial data. A drug's actual contribution to patient care evolves during the post-marketing period when widespread clinical experience reveals new uses, adverse effects, and other new information. The accuracy of any assessment of a drug's contribution to medical care not only increases with time, clinical use, and the amount of research performed on the drug, but is also determined by the practicing physician who is faced with the need to individualize patient therapy.

Even if the basis for the staff's analysis were valid, a careful analysis of the data clearly shows that the pharmaceutical industry is successfully developing new products considered to represent therapeutic advances, both by the FDA as well as by current standards of physician care. A review of the data, founded in a more thorough understanding of the research and regulatory process, can only conclude that the large research expenditures made by the pharmaceutical industry have resulted in, and will continue to result in, important new drugs for the treatment of the fatal and disabling diseases that plague Americans.

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MG

November 13, 1989

The Honorable David Pryor
Chairman
Senate Special Committee on Aging
Room G-31
Dirksen Building
Washington, D.C. 20510

Dear Senator Pryor:

Thank you for your special interest in the cost of medicine for Myasthenia Gravis patients.

Over the last two years, our patients have been victimized by enormous price increases. These increases resulted from the sale of the U.S. and Canadian distribution rights to the medications Mestinon and Prostigmine.

Originally, our patients received low cost medications through our drug banks as a result of special contracts granted by Hoffman-LaRoche Pharmaceuticals. In 1988, ICN Pharmaceuticals purchased the exclusive distribution rights from Hoffman-LaRoche. Within 10 months of that purchase, ICN discontinued all special contracts. Our patients suffered dramatically from a price increase of more than 150 percent.

Patients like Mr. Jake Green had been spending nearly $400 each year on medications available through our drug banks. Suddenly, as the contracts expired, they had to spend approximately $1,000 a year for their life-sustaining medication.

Last week we were informed that the price of this expensive, but essential, medication will be increased a minimum of an additional 8 percent.

Myasthenia Gravis is a serious, potentially life-threatening autoimmune neuromuscular disease. There is no cure. The prevalent treatment is control of symptoms with medication such as Mestinon.

The Myasthenia Gravis Foundation applauds your efforts to find ways to reduce these prescription drug costs and to make pharmaceutical companies accountable for price increases.

We welcome the opportunity for Mr. Green to present his case on behalf of all myasthenic patients. And, we appreciate your invitation for the Myasthenia Gravis Foundation to participate in your November 16 Senate Hearing on this urgent problem.

Sincerely,

Roger D. Allan

Roger D. Allan
President

RDA/ae

MYASTHENIA
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An Autoimmune Neuromuscular Disease

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FOR IMMEDIATE RELEASE
November 14, 1989

FOR FURTHER INFORMATION, Contact
Ann VanderMeer-Robinson
800-541-5454 or 312-427-6252

Mr. Jake Green's life is being threatened by the rising profits of the pharmaceutical industry. Jake has Myasthenia Gravis and is the victim of the profiteering attitude of the pharmaceutical companies that make and distribute his only life-sustaining medication. La Roche and ICN Pharmaceuticals have been increasing the cost of Mestinon by nearly 200% since 1987. In May of 1989 ICN denied any continuation of special pricing that allowed for Mr. Green to get his medication at a reduced cost through an MGF drug bank. Mr. Green had paid $40 for this essential medication through the drug bank and after May he was forced to pay $87. Today Mr. Green was told that he would be pay 8% more as of December 1, an increase of 150% in seven months. If Mr. Green had not used the MGF drug bank and had gone to his local pharmacy he would have paid $66 in September of 1988 and $130 today, and a higher price after December 1, 1989.

Mestinon is the only medication that relieves his MG symptoms; there is no generic substitute and La Roche and ICN are the only companies that make and distribute Mestinon in the United States. Jake's life will always be dictated by the disease and the pharmaceutical industry which can increase the cost of his medication without any regulation.

MG

53 W. Jackson Boulevard, Suite 1352, Chicago, IL 60604 (312) 427-6252
(800) 541-5454
Research • Education and Information • Patient Services Fax - (312) 427-8437

The Myasthenia Gravis Foundation has recently taken a position to reject a sustaining grant from ICN Pharmaceuticals in light of of their appalling disregard for the plight of their patients. In their communication the Myasthenia Gravis Foundation has requested the elimination of the 8% increase and the reinstatement of the special contract.

Myasthenia Gravis is a potentially life-threatening autoimmune disease that affects approximately 100,000 Americans. This disease affects the voluntary muscles that control one's breathing, walking, talking, or eating because of a decrease in message received by the muscles from the nerves. There is no cure.

The US Senate Special Committee on Aging subcommittee, chaired by Senator David Pryor, will be hearing testimonies by Mr. Jake Green and others affected by the reckless profiteering of pharmaceutical companies. The hearings will be held at 9 a.m. on November 16, in Room SD-628 of the Dirksen Senate Office Building in Washington, D.C.

Mr. Green and Mr. Roger Allan, president of the Myasthenia Gravis Foundation, will be available for questions and answers from the press after the hearing in the hall outside the hearing room.

THE ESTIMATED COST OF A MYASTHENIC PATIENT

Rx America's 1989 Prices
(Retail Drug Store Prices)

MEDICATION	LOW	MIDDLE	CRITICAL
1. MESTINON 60 mg. Per Pill = $0.174(.266) 100 tabs = $17.40 (26.60) 500 tabs = $87.00 (133.00)	4 tablets daily Daily $.69 (1.06) Monthly $21.17 (32.36) Yearly $254.04 (388.36) 20 Years $5080.80(7767.20)	10 tablets daily Daily $1.74 (2.66) Monthly $52.92 (80.90) Yearly $635.10 (970.90) 20 Years $12,702 (19,418)	20 tablets daily Daily $3.48 (5.32) Monthly $105.84 (161.81) Yearly $1270.08 (1941.80) 20 Years $25,401 (38,836)
2. PREDNISONE (Rx America Prices) 10 mg = $.0175 per pill $1.75/100 tabs 20 mg = $.032 per pill $3.20/100 tabs 50 mg = $.127 per pill $12.70/100 tabs	10 mg. every other day Daily = $.0175 Monthly = $.28 Yearly = $3.36 20 Years = $67.20	30 mg. every other day Daily = $.05 Monthly = $.80 Yearly = $9.60 20 Years = $192.00	100 mg. a day Daily = $.25 Monthly = $7.11 Yearly = $85.34 20 Years = $1,706.80
3. IMURAN 50 mg. Per Pill = $.7295(.8969) 100 tabs = $72.95(89.69)	1 tablet daily Daily = $.72(.8969) Monthly = $20.16(27.28) Yearly = $241.92(327.37) 20 Years = $4,838.40(6547.36)	2-2½ tablets daily Daily = $1.82(2.2423) Monthly = $51.07(68.20) Yearly = $612.78(818.44) 20 Years = $12,255(16,368)	4 tablets daily Daily = $2.918(3.5876) Monthly = $81.70(109.123) Yearly = $980.45(1309.474) 20 Years = $19,608(26,189)
4. *Cyclosporine 1 ml = $4.00 50 ml = $200.00 a bottle	.8 ml twice a day Daily = $6.40 Monthly = $179.20 Yearly = $2,150.40 20 Years = $43,008.00	1.5 ml twice a day Daily = $12.00 Monthly = $336.00 Yearly = $4,032.00 20 Years = $80,640.00	2.5 ml twice a day Daily = $20.00 Monthly = $560.00 Yearly = $6,720.00 20 Years = $134,400.00

*NOT RX AMERICA'S PRICES

HOSPITALIZATION

1. **THYMECTOMY**

1. Transternal - Surgery Fee = $10,000
Surgeon Fee = $ 2,000
Intensive Care (2 days) = $ 2,700
Hospital Bed (6 days) = $ 3,000
$17,700

1-3 days intensive care required =
$1,200 - $1,500 a day

5-7 days in regular hospital bed =
$500 a day

2. Transcervical - Surgery Fee = $3,000
Surgeon Fee = $2,000
Intensive Care (1 day) = $1,350
Hospital Bed (3 days) = $1,500
$6,850

NOT AS COMMON
1 day intensive care stay at $1,200-$1,500 a day
2-3 Hospital stays at $500.00 a day

2. **PLASMAPHERESIS**

PLASMAPHERESIS	NOT A CRISIS	CRITICAL CONDITION	CRISIS
Cost per exhange = $1,200 - $2,000 Average - $1,600	3X a week for 1st week 2X a week for 2nd week 1X a week for 3-6 months 18-22 exchanges = 20 exchanges @ $1,600 = $32,000.00	2X a week for 6 months 48 exchanges = $76,800	3-4X a week for 2 weeks Refer to #1 24-30 exchanges (24 exchanges @ $1,600)= $54,400.00

3. **RESPIRATORY CRISIS**

- varies 6 weeks to 6 months
- average hospital stay is 2 months
- 7-14 days in intensive care at $1,350 a day = $14,175.00
- plasmapheresis maybe required (1 exchange) = $ 1,600.00
- 14-21 days in hospital bed at $500 a day = $ 8,750.00

$24,525.00 at an average price

- price does not include medications

4. **MEDICATION ADJUSTMENT**
(if patient 's on steroids)

- average hospital stay is 7 days at $500 per day = $3,500.00
- price not including medication
- price not indicating if problem occurs and more treatment is necessary

DIAGNOSIS
(including doctors fee)

Tensilon = $150-200
Antibody = $265-300 (Includes lab fee of $100-$150)
EMG = $240-300 ($120 per extremity)

DOCTORS VISIT
Cost: New = $120-$200
Follow-up = $50.00

LOW	MIDDLE	CRITICAL
Once every 6 months	Every 3-4 months	Once a week
New = $160.00	New = $160.00	(No indication of how long a patient must continue to see a doctor once a week)
Return = $50.00	3X = $150.00	
$210.00	$310.00	
2 return = $100.00	4X at return price = $200.00	Once a week = $ 50.00 Monthly = $ 200.00 Yearly = $2400.00

MYASTHENIA GRAVIS FOUNDATION FACT SHEET: INCREASES IN PRESCRIPTION DRUG COSTS

Dosage: 16 pills per day, 500 pills per month required to control Myasthenia Gravis for Mr. Jake Green.

Cost of medication, through MGF, for 500 tablets:

1987 $33 per order, $396 per year.

1988, August Hoffman-LaRoche sells U.S. and Canadian distribution rights to ICN, Costa Mesa, CA. (Sale covers rights to Mestinon 60 mg, Mestinon 180 mg, Prostigmine.) During, the the next 10 months, ICN continued to honor Hoffman-LaRoche's special contracts to provide drugs to MG patients at reduced rates.

1989, May - Renewal of special contracts ceases.

1989, June - MGF launches national prescription service. Mestinon price becomes $87, subsidized through the national foundation. ($1000 per year.)

1989, Nov. - ICN notifies wholesalers that, effective December 1, 1989, there will be an 8% increase for the MG medications. ($1100 per year.)

Note: Patients have always had two ways to obtain their drugs, through the MG Foundation or at a local pharmacy. Over the two-year period described above, a patient purchasing his or her Mestinon at a local drug store would have spent $780 in 1987 and $1500 in 1989.

The same patient purchasing through the Myasthenia Gravis Foundation would have spent $396 in 1987. As of December 1, that cost will increase to $1100 per year.

Estimated number of people with Myasthenia Gravis - 100,000.

STATE OF CALIFORNIA—HEALTH AND WELFARE AGENCY
GEORGE DEUKMEJIAN, Governor

DEPARTMENT OF HEALTH SERVICES
714/744 P STREET
P.O. Box 942732
SACRAMENTO, CA 94234-7320
(916) 322-5824

November 14, 1989

The Honorable David Pryor
United States Senate
Attn: David Schulke
Senate Committee on Aging
Senate Office Building
Washington, DC 20510

Dear Senator Pryor:

I wish to thank you very much for the opportunity to tell you about a program that has the potential of saving California taxpayers millions of dollars as well as improving the availability of pharmaceuticals to those California citizens most in need, the Medi-Cal beneficiaries. The following comments and information addresses what the California Medicaid Program (Medi-Cal) pays for prescription drugs, and what steps are being considered in order to bring what this program pays in line with other third party payors.

Currently, the Medi-Cal program spends over 150 million dollars per year on providing single source prescription drugs manufactured by approximately 50 companies to our beneficiaries. In paying average wholesale or "list" price for these single source drugs, Medi-Cal pays 20 percent to 80 percent more than other publicly funded health programs. The reason for this disparity is that Medi-Cal does not receive any of the rebates or discounts that are available to other publicly funded programs such as the State Department of General Services, the Veterans Administration, the Department of Defense and Los Angeles County. Under the Medi-Cal Drug Manufacturer Discount Program, we will be able to benefit in a similar manner from some of the types of cost saving agreements enjoyed by these agencies.

The discount program will be implemented in two phases. First, using current authority found in program regulations, the Medi-Cal program will negotiate with drug manufacturers who have petitioned to have their drugs added to the Medi-Cal Formulary. At the present time, petitions to add drugs which have a positive fiscal impact on the Medi-Cal program to the formulary are being denied. The Department will seek to mitigate the fiscal impact of any formulary additions through discount contracts. The discount contract would provide that the pharmaceutical manufacturer "discount" to the State a percentage of total expenditures for the specific drug once the drug is added to the Formulary.

The second phase will be directed at those pharmaceutical manufacturers who currently have drugs on the Medi-Cal Formulary. These manufacturers will be invited to enter into discount contracts with the State. If this approach is unsuccessful, then strategies to encourage competitive pricing between both Formulary and non-Formulary drug manufacturers will be implemented. Subsequently, if necessary, Formulary regulations will be amended to add and/or delete drugs, based upon the resultant savings.

During the last legislative season, the Department of Health Services (DHS) sponsored legislation (AB 2148) which would have resulted in a minimum of $40 million in savings to the Medi-Cal program. Unfortunately this progressive legislation was defeated in the Assembly Health Committee following intense lobbying by the pharmaceutical industry. The Drug Manufacturer Discount Program we are currently implementing will be a longer and slower process that will not generate the type of immediate savings envisioned in AB 2148; however, it is a program that still possesses great benefits.

It is not the goal of the drug discount program to "get drugs off" or reduce the size of the Medi-Cal Formulary. The Department recognizes the distribution and other associated industry costs that make up the price Medi-Cal pays. These factors, however, will be considered during negotiations. The Department also recognizes that California's tax-funded Medi-Cal program for the poor is paying considerably more for pharmaceuticals than any other governmental program.

With drug discount contracts in place, the Department will be able to utilize tax dollar savings to offset the higher cost of newer generation pharmaceuticals or utilize the savings in other areas of critical program need. The beneficiaries of this program will be both Medi-Cal recipients, who will have access to the latest and most improved medications, and the California taxpayers, who will see more effective use of their tax dollar. I have enclosed additional background information on the Drug Manufacturers Discount Program which provides more detail.

I hope this information has been of assistance to you. My staff and I will be very happy to discuss this issue with you and we remain available to provide you with any necessary information or support.

Sincerely,

John Rodriguez
Deputy Director
Medical Care Services

Enclosures

MEDI-CAL DRUG DISCOUNT PROGRAM BACKGROUND

Medi-Cal program expenditures have risen dramatically the past decade. Even more alarming is the rate at which drug program expenditures have risen compared to all other services of the Medi-Cal program. Chart #1 illustrates the problem that has been occurring with respect to California Medi-Cal. It is interesting to note that since FY 78-79, drug program expenditures have increased 150%, while all other services have only climbed 50%!

A significant reason for this rise in drug expenditures is the fact that we are paying top dollar for single manufacturer type drugs; whereas, many other major governmental health programs negotiate discount prices considerably less than what Medi-Cal pays for the same drugs. The Department of General Services, the Veterans Administration, and Los Angeles County, for example, have long-standing negotiated drug price discounts for single manufacturer drugs as well as drugs that are available generically. Chart #2 illustrates the extremely high prices that Medi-Cal pays compared to other governmental program. While this chart only lists six drugs as examples, there are many other drugs which also have significant price differentials. As shown in Chart #3, these differentials, at least as reflected in the list of the top 50 drugs in dollar volume, can be very drastic. The state is now actively taking steps to implement a new cost effective approach to how it purchases these drugs so that the California taxpayer is not forced to pay such excessive prices in the future.

The Medi-Cal program is a very large purchaser of drugs, although overall it comprises a small percentage of the manufacturers national or even state market share. Our total expenditures are over $600 million/year of which over $150 million is devoted to single source pharmaceuticals. The intention of the Drug Manufacturers Discount Program is to receive the most favorable prices for single manufacturer drugs on the Medi-Cal Drug Formulary. These prices should be comparable to prices offered by manufacturers to other governmental health programs.

This discount concept would have no effect on the normal distribution of drugs to pharmacies by drug manufacturers and wholesalers. The mechanism for this discount program is very simple. Based upon the negotiated contract amount, (which would be a set percentage of reimbursement), and Medi-Cal drug utilization data, the Department would merely bill manufacturers on a quarterly, semi-annual, or annual frequency for the discount amount due to the Department. This would be after the dispensing of the medication to the beneficiary and reimbursement to the pharmacy provider of the prescribed single source drug.

There are several questions and concerns about the Drug Discount Program that have been raised which should be addressed. One important question is, how will the discount program benefit Medi-Cal patients. The answer is that savings generated through discounts will allow us to expand the number of single manufacturer drug products on the Medi-Cal Drug Formulary. Decisions to not include drugs on the formulary are usually made on the basis that the drug in question is no better or worse than similar drugs on the Formulary but is more expensive. Manufacturer discount contracts would allow for such drug additions to the Formulary by providing fiscal savings instead of cost to the Medi-Cal program.

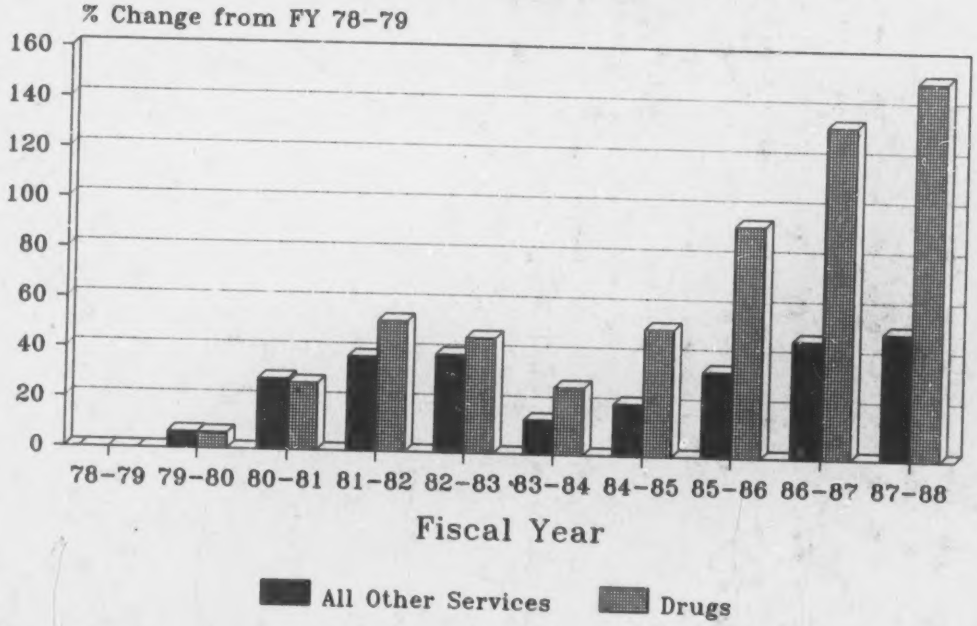
Another question is, what is the likelihood of drug manufacturers entering into these discount contracts? The answer is that there is high potential for such contracts to occur. Due to the fierce competition among drug manufacturers and the large volume of drugs used under the Medi-Cal program, it is of great importance to manufacturers to have their products listed on the Formulary. Furthermore, contracting with government health programs is commonplace for drug manufacturers (e.g., contracts with the U.S. Veterans Administration, the State Department of General Services, Los Angeles County, etc.)

One additional concern, which has often been presented by drug manufacturer representatives, is that because this discount proposal doesn't involve the Department taking possession of the drugs, as is the case with manufacturer contracts with other governmental programs, the overhead costs associated with distribution would not allow for large discounts. First of all, this assertion is not accurate because not all government contracts involve taking possession of drugs. The State Department of General Services, for example, contracts with manufacturers for large discounts, but the drugs are distributed to the State hospitals through a wholesaler. Secondly, the cost of distribution is an element that the contract negotiator would take into consideration. It is maintained that a significant discount is appropriate for a payer like Medi-Cal that has a drug budget of over 1/2 billion dollars.

In summary, it is time for California and other Medicaid programs to move forward with this concept of discount pricing. The period when tax supported health programs for the poor and elderly are forced to pay "top dollar" for pharmaceuticals should end, and such programsshould be allowed to enter into the discount market as have other third party payers. Such efforts should be supported by the Federal Medicaid system even to the point of legislatively mandating that state Medicaid programs participate in such discount efforts. The task of implementing such a program will be difficult, but it is one that the California Medi-Cal program is committed to. It is strongly felt that such a program will result in significant program savings and provide a wider range of pharmaceuticals for Medi-Cal's 3 million beneficiaries. Support on the national level is needed and appreciated.

RI:rc/dw370

Medi-Cal Drug Expenditures
Percent Change From FY 78-79



Source: Medi-Cal Claims Payment Data

Chart #1

Medi-Cal Prices Compared to Prices Paid by Other Organizations

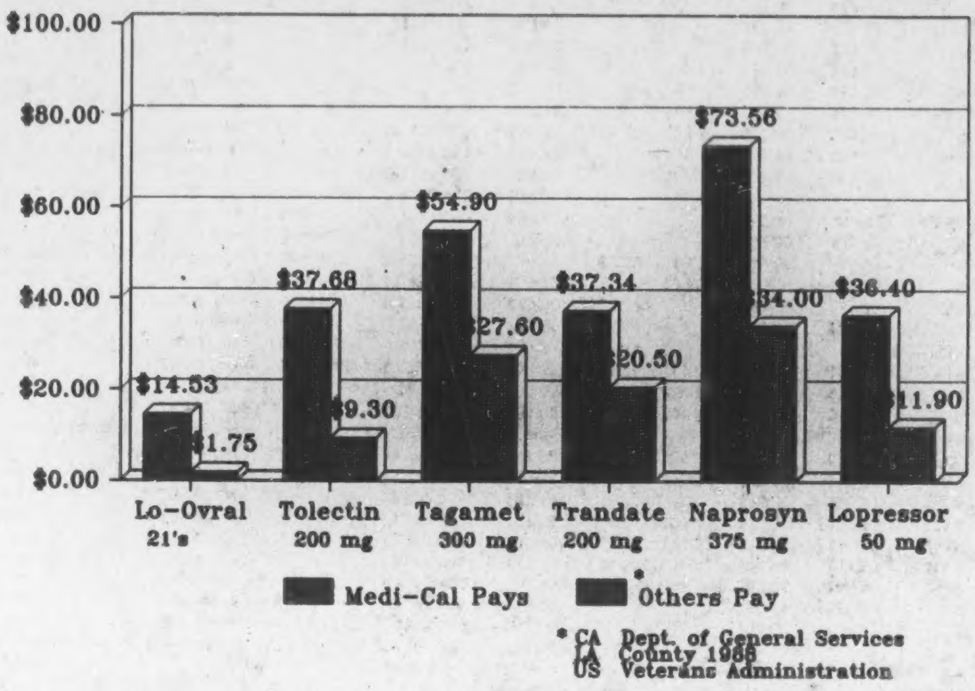


Chart #2

Sole Source Drugs - Price Paid Comparison - Top 50 by Dollar Volume

Drug Name	Manufacturer	Amt Paid	Medi-Cal Pays	General Services	LA County	Veterans Admin	Lowest	Percent Difference
Premarin Vaginal Cream w/ Applicator	Ayerst	$281,826	$15.80					
Imuran 50mg Tablet	Burroughs-Wellcome	$513,599	$65.66			$58.98	$58.98	11%
Retrovir 100mg Capsule	Burroughs-Wellcome	$2,591,695	$180.29			$150.24	$150.24	20%
Zovirax 200mg Capsules	Burroughs-Wellcome	$559,452	$63.96			$63.96	$63.96	0%
Lopressor 100mg Tablet	Geigy	$1,171,480	$55.71	$39.03	$36.46	$11.90	$11.90	368%
Lopressor 50mg Tablet	Geigy	$1,299,624	$36.40	$24.13	$21.52	$11.90	$11.90	206%
Ceclor Pulvule 250mg	Lilly, Eli	$1,750,284	$127.83		$101.13		$101.13	26%
Carafate 1gm Tablet	Marion Labs	$2,952,258	$47.19			$28.51	$28.51	66%
Cardizem 30mg Tablet	Marion Labs	$2,774,441	$29.38		$23.75	$17.50	$17.50	68%
Cardizem 60mg Tablet	Marion Labs	$4,571,997	$46.88		$38.50	$28.60	$28.60	64%
Haldol 50mg/ml Ampule (Decanoate)	McNeil Labs	$481,399	$211.86	$143.00		$122.91	$122.91	72%
Tolectin DS 400mg Capsule	McNeil Labs	$1,692,161	$61.92		$18.00	$15.60	$15.60	297%
Clinoril 150mg Tablet	Merck Sharp & Dohme	$807,609	$60.53	$55.53	$50.48		$50.48	20%
Clinoril 200mg Tablet	Merck Sharp & Dohme	$2,783,451	$74.38	$68.24	$62.04	$59.00	$59.00	26%
Sinemet-10/100 Tablet	Merck Sharp & Dohme	$554,712	$32.33	$28.11		$9.15	$9.15	253%
Sinemet-25/100 Tablet	Merck Sharp & Dohme	$890,510	$35.92	$35.92		$35.52	$35.52	1%
Sinemet-25/250 Tablet	Merck Sharp & Dohme	$783,681	$42.55	$39.37		$41.28	$39.37	8%
Timoptic 0.5% Ocumeter 10ml	Merck Sharp & Dohme	$1,432,995	$19.72		$17.88		$17.88	10%
Timoptic 0.5% Ocumeter 5ml	Merck Sharp & Dohme	$378,997	$10.17	$9.59	$9.22	$9.86	$9.22	10%
Vasotec 10mg Tablet	Merck Sharp & Dohme	$512,737	$57.25			$56.68	$56.68	1%
Vasotec 5mg Tablet	Merck Sharp & Dohme	$807,067	$54.52			$50.44	$50.44	8%
Monistat-Derm 2PC Crm 85 gm	Ortho Pharmaceutical Corp	$283,946	$24.60					
Feldene 10mg Capsule	Pfizer Labs	$263,602	$83.58		$69.38	$66.00	$66.00	27%
Feldene 20mg Capsule	Pfizer Labs	$7,015,269	$143.02		$118.73	$86.00	$86.00	66%
Procardia + Adalat 10mg	Pfizer Labs	$8,424,026	$36.59	$25.90	$23.60	$22.00	$22.00	66%
Procardia + Adalat 20mg	Pfizer Labs	$850,324	$65.86		$46.62	$39.61	$39.61	66%
Accutane 40mg Capsules	Roche Labs	$377,043	$71.04			$62.30	$62.30	14%
Klonopin 0.5mg Tablet	Roche Labs	$492,253	$42.41			$37.22	$37.22	14%
Klonopin 1mg Tablet	Roche Labs	$356,222	$48.40			$42.47	$42.47	14%
Klonopin 2mg Tablet	Roche Labs	$294,921	$67.09			$58.86	$58.86	14%
Geocillin 382 Mg Tablet	Roerig, Div. Of Pfizer	$244,150	$97.20			$53.40	$53.40	82%
Glucotrol 10mg Tablet	Roerig, Div. Of Pfizer	$519,337	$36.18	$32.20		$24.90	$24.90	45%
Glucotrol 5mg Tablet	Roerig, Div. Of Pfizer	$575,542	$19.71	$17.54		$13.26	$13.26	49%
Methergine 0.2mg Tablet	Sandoz Pharmaceuticals	$278,626	$28.80					

Chart #3

Sole Source Drugs – Price Paid Comparison – Top 50 by Dollar Volume

Drug Name	Manufacturer	Amt Paid	Medi-Cal Pays	General Services	LA County	Veterans Admin	Lowest	Percent Difference
Parlodel 2.5mg Tablet	Sandoz Pharmaceuticals	$291,840	$100.98	$64.67		$49.13	$49.13	106%
Compazine 25mg Supp	Smith, Kline & French Lab.	$553,356	$22.50			$19.13	$19.13	18%
Tagamet 300mg Tablet	Smith, Kline & French Lab.	$14,964,368	$54.90	$45.37	$42.52	$29.20	$29.20	88%
Tagamet 400mg Tablet	Smith, Kline & French Lab.	$6,334,983	$55.65	$44.20	$48.04	$49.80	$44.20	26%
Capoten 12.5mg Tablet	Squibb, E.R. & Sons	$855,400	$31.10			$28.77	$28.77	8%
Capoten 25mg Tablet	Squibb, E.R. & Sons	$2,483,094	$34.24			$28.67	$28.67	19%
Capoten 50mg Tablet	Squibb, E.R. & Sons	$1,058,319	$57.08			$53.15	$53.15	7%
Naprosyn 250mg Tablet	Syntex Labs	$3,273,011	$57.76	$45.37	$42.52	$29.20	$29.20	98%
Naprosyn 375mg Tablet	Syntex Labs	$8,116,533	$73.56	$57.78	$55.56	$34.00	$34.00	116%
Naprosyn 500mg Tablet	Syntex Labs	$4,482,075	$90.68	$71.23	$68.48	$41.00	$41.00	121%
Tri-Norinyl Tablet 28's	Syntex Labs	$449,352	$14.79					
Halcion 0.25mg Tablet	Upjohn	$602,946	$34.10	$27.22		$11.15	$11.15	206%
Halcion 0.5mg Tablet	Upjohn	$401,767	$29.72	$29.72		$12.50	$12.50	138%
Plaquenil 200mg Tablet	Winthrop-Breon Labs	$270,288	$60.67			$59.60	$59.60	2%
Lo Ovral Tabs 0.3-30mcg -28's	Wyeth Labs	$642,450	$14.71	$1.75			$1.75	741%
Lo/Ovral-21 Tablet	Wyeth Labs	$942,167	$14.53	$1.75			$1.75	730%
Ovral-21 Tablet	Wyeth Labs	$337,401	$16.72	$1.75	$1.75		$1.75	855%

"Average" percent savings 112%

ICN Pharmaceuticals, Inc.

3300 Hyland Avenue
Costa Mesa, California 92626
Telephone: (714) 545-0100
Telex: 67-0413

November 15, 1989

Senator David H. Pryor
Chairman
U.S. Senate Special Committee on Aging
Washington, D.C.

Dear Sen. Pryor:

ICN Pharmaceuticals is a small, California-based pharmaceutical company that makes, markets and sells 300 pharmaceutical products in the United States and internationally. The company has been in business for 30 years and over this period has developed and gained commercial authorization to market a number of useful therapeutic compounds. The company is research-based and over the past decade has invested over $150 million in research and development for new pharmaceuticals, principally antivirals.

ICN is a socially responsive company whose main mission is to improve the health of mankind through the development and distribution of useful pharmaceutical therapies. This is embodied in the company's motto: "He who has health has hope and he who has hope has everything." As the founder of the company and an immigrant who fled from communism, I have a profound belief and respect for the American political system, and welcome the opportunity to respond to any and all questions that have been asked of us by the committee staff on our marketing practices for the drug Mestinon. My only regret is that due to the distance involved and the short notice of the hearing we received, I am unable to appear in person.

In line with the company's philosophy, let me say immediately at the outset that it is the company's policy that no patient will ever be denied a drug marketed by ICN because of his or her inability to pay. This policy applies to Mestinon, which is used in the chronic treatment of Myasthenia Gravis. ICN maintains an indigent patient program whereby patients can obtain Mestinon free of charge. Any patient who is not able to afford their medication, who does not have health insurance, or who has had Mestinon purchases rejected for coverage by their health insurance can receive their drug free of charge. Currently, 285 patients, representing approximately five percent of all Mestinon-treated patients, receive their drug at no charge through this program.

Our indigent program is very simple. All a patient has to do is give us a request signed by the patient and his or her physician. In some instances, a copy of the patient's health plan indicating it doesn't cover prescriptions is needed. We don't check further. No questions asked.

The committee staff has expressed interest about Mestinon, its price and the way the drug is marketed. The most useful way to respond to these areas of inquiry is to recount ICN's history with the drug to date.

At the time, ICN's hospital sales force had only one product to sell, an antiviral agent used in the treatment of hospitalized infants with severe respiratory disease. As part of a strategy to increase the number of products marketed by the company's hospital sales force, ICN acquired the U.S. marketing rights to Mestinon from F. Hoffmann-La Roche & Co. in June of 1988. The addition of products like Roche's line of anticholinesterase products, of which Mestinon is a part, makes the sales force more cost-efficient by spreading overhead over more products. This makes it more economical to maintain a hospital sales force.

ICN's licensing strategy is based on licensing products with smaller sales volumes. Simply put, we believe it makes more sense for small companies to handle smaller products and bigger companies to handle larger products. Big companies are better equiped to maintain large national and international distribution systems for products with large patient bases. Small products often get lost in larger companies. Big companies often do not pay much attention to smaller products. Small companies can.

Mestinon is a case in point. [redacted] The average cost of Mestinon approximates $600 a year. In November of this year, a price increase of 8 percent was announced by the company. While we cannot address the pricing history of this drug before we obtained our licensing rights, this will be the first price increase in the 16 months since ICN assumed U.S. marketing rights.

Although the 8 percent increase approximates inflation, it was really intended to offset the cost of capital improvements necessary for ICN to produce Mestinon. It also allows us to initiate research into a new uses for Mestinon. Through this effort, myasthenia gravis patients, as well as patients in an entirely different disease category, may ultimately benefit from the fruits of this research. Moreover, the price increase allows the company to produce and distribute an educational videotape to physicians, such as opthomologists, most likely to encounter undiagnosed patients early in their disease. We believe that half the actual number of myasthenia gravis cases in the U.S. are currently undiagnosed.

The committee staff has asked why the drug bank contracts were allowed to expire. In essence, the drug banks involve a two-tier pricing system. Following a review of the drug bank system in July of 1988, we determined that this pricing strategy was not conducive to the way ICN believes it should conduct its business. Our policy is to have one price for each of our products to the same class of customers. Under the two-tiered pricing system in effect under the drug banks, local drug stores are at a competitive disadvantage to larger institutions receiving price breaks under the "drug bank" system. This is not consistant with the American economic system and it is against our general business policy as a company.

Ninety percent of patients in the drug banks are covered by private and public health care plans. Because we recognized that the expiration of the drug bank contracts could possibly provide hardship to some, we provided a grant to Myasthenia Gravis Foundation, part of which was to be used to subsidize patients using the drug banks. Most important, the indigent program is open to all patients, including former drug bank users.

Since acquiring the licensing rights, we have attempted to work closely with the Myasthenia Gravis Foundation. We have repeatedly asked the foundation for suggestions as to what contributions the company can make toward helping for the care and treatment of Myasthenia Gravis patients. Consequently, a $50,000 grant was awarded to the foundation in 1989 to support patient services, public and medical education and research. This grant is intended to be ongoing and the amount of future installments is currently under review.

November 15, 1989
Senator David H. Pryor
Page four

In summary, since the company obtained licensing rights to Mestinon, ICN has had concern that some patients, particularly those on fixed incomes without health insurance, may find it difficult to afford the drug. In order to avoid placing undue burden on these patients and any other patients who, for whatever reason, may feel a financial strain in obtaining their medication, ICN has made and will continue to make Mestinon available at absolutely no charge. We believe this action meets the needs of all Myasthenia Gravis patients, and is in line with our general corporate philosophy and the country's health care objectives.

We would be more than happy to answer any questions raised by the contents of this letter as well as to continue further dialogue with the Myasthenia Gravis Foundation in the interest of MG patients.

Sincerely,

Milan Panic

Milan Panic
Chairman and Chief
Executive Officer

MP:sab

Pharmaceutical
Manufacturers
Association

Gerald J. Mossinghoff
PRESIDENT

November 15, 1989

The Honorable David Pryor
Chairman
Special Committee on Aging
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

Committee staff have advised my office of your plans for an informal discussion involving Senators, staff, witnesses and others interested in the issues following the Committee's November 16 hearing relating to prescription drug prices.

I regret it will not be possible for me to participate in the discussion as I will be out of the country attending a meeting of the European Federation of Pharmaceutical Industries' Associations. Ordinarily, in similar circumstances I would cancel that trip. However, given the importance to our industry of developments in the European Economic Community and our long-time efforts to become more actively involved in the EFPIA, I feel it is necessary to go ahead with that commitment.

PMA staff will be attending both the hearing and the subsequent discussion, but in accordance with long-standing PMA policy, they will not have the approval of the Board of Directors to speak for the Association at that meeting.

Sincerely,

Gerald J. Mossinghoff

1100 Fifteenth Street NW, Washington, DC 20005 • Tel: 202-835-3420 • TWX: 7108229494-PMAWSH

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United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

November 27, 1989

Mr. R. Michael Berryman
Director of Pharmacy
Community Memorial Hospital
126 Buena Vista Circle
South Hill, Virginia 23970

Dear Mr. Berryman:

Many thanks for testifying at the November 16 hearing of the Senate Special Committee on Aging on the high costs of prescription drugs. Your testimony was essential to the Committee gaining an understanding of the impact rising prescription drug costs are having on Virginia's Medicaid program and the strategies the Commonwealth is considering to help control these costs.

I also would like to take this opportunity to share with you a copy of the Committee staff report from the July 18, 1989 hearing on this subject, and the November 16 hearing. We would welcome any comments you might wish to make regarding these reports.

We will be sure to forward you a copy of the hearing record print as soon as it is available. Again, we appreciate your valuable contribution to the hearing and hope to continue working with you on this issue of mutual concern.

Sincerely,

David Pryor

David Pryor
Chairman

Enclosures
DP/jm

MGA
MYASTHENIA GRAVIS ASSOCIATION, INC.
8131 WEST OUTER DRIVE / DETROIT, MICHIGAN 48235 / 927-7633
United Way Agency

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Deborah Kent
Executive Director

United Way Supported Service

November 29, 1989

Mr. David Pryor
United States Senate
Chairman
Special Committee on Aging
G-31-SDOB
Washington, D.C. 20510-6400

Dear Senator Pryor,

Thank you for holding a Senate Investigative Hearing on the rising cost of prescription medications on November 16th. As the Executive Director of the Detroit Chapter Myasthenia Gravis Foundation, I can site numerous examples similar to the testimony of myasthenia gravis (MG) patient Mr. Jake Green. As you learned MG is a neuromuscular chronic illness that is controlled by a strict regimine of medication. The proposed 8% increase by ICN Pharmaceuticals on the drug Mestinon will definitely cause hardship to a large segment of our patient population.

I am very appreciative of your and the committee's concern. On behalf of our patients, thank you.

Sincerely,

Deborah Kent

Deborah Kent
Executive Director

DK/mh
cc: Jim Woods
National MGF Executive Director

dp dANIELS
pHARMACEUTICALS, INC.

December 11, 1989

Senator David Pryor
Chairman
Special Committee on Aging
U.S. Senate
267 Russell Building,
Washington, DC 20510

Dear Senator Pryor:

Reference is made to the hearing held on November 16, 1989 by the U.S. Senate Special Committee on Aging entitled "Skyrocketing Prescription Drug Prices: Turning A Bad Deal Into A Fair Deal". The coverage by the trade publication FDC Reports "The Pink Sheet" attracted my attention and prompted my writing of this letter to you.

As the President of a small pharmaceutical company I can advise you of drug products other that those you have targeted in your hearings which equally put financial strain on the health care delivery system in the United States. My company markets a brand of levothyroxine at one third of the price as the market leader Synthroid (Boots-Flint) brand of levothyroxine. This drug is considered a "grandfathered" product because it has been on the market since before 1938 which as you know is when the Food, Drug and Cosmetic Act was enacted. Since such drugs are generally recognized as safe and effective they are marketed without premarket approval. Therefore the development costs are not anywhere as burdensome or costly as a true innovator product. Boots-Flint has marketed this product for over 30 years as its previous corporate entity.

In 1988 Synthroid was the thirteenth most actively prescribed drug according to American Druggist, February 1989 (Exhibit 1). It is the market leader for the treatment of hypothyroidism, showing a sales volume of approximately 90 million dollars as compiled by IMS America (Exhibit 2). Boots-Flint has continually raised the prices of the various potencies by approximately 20% per year according to Medi-Span (Exhibit 3). In fact they are such an attractive investment based on this highly profitable branded generic drug that the Flint Labs prescription division of Baxter Travenol was acquired by Boots in August of 1986 for the unheard of price of $550 million dollars. Please refer to Exhibits 4 and 5 which describe this deal.

According to the above cited articles "in 1985 Flint had pretax earnings of $33.1 mil., which was 61.6% of sales totalling $53.7 mil." and "83% of Flint's sales come from a drug, no longer under patent, to treat thyroid deficiency." This drug is a maintenance drug which must be used daily for life from the time the disease is diagnosed. It is quite evident that many elderly patients now take this drug with many more to be added to the Medicare program as the population ages.

If you or members of your staff would like any further information please feel free to contact me.

Respectfully yours,

DANIELS PHARMACEUTICALS, INC.

Bernard D. Wolfson, Ph.D.
President

BBW/bd

Enclosures

c.c. Senator Bob Graham
325 John Knox Road
Tallahassee, Florida 32303

3030 Federal Building
Little Rock, Arkansas 72201

Exhibit 1.

TOP 200 PRESCRIPTION DRUGS DISPENSED IN U.S. COMMUNITY PHARMACIES BRAND NAME AS DISPENSED, NEW AND REFILL PRESCRIPTIONS—ALL STRENGTHS

1	2	Amoxil	Beecham
2	3	Lanoxin	Burroughs
3	4	Xanax	Upjohn
4	9	Zantac	Glaxo
5	10	Premarin	Ayerst
6	1	Dyazide	SKF
7	5	Tagamet	SKF
8	8	Tenormin	ICI Pharma
9	14	Naprosyn	Syntex
10	17	Cardizem	Marion
11	6	Tylenol w/Codeine	McNeil
12	20	Seldane	Merrell Dow
[redacted]	[redacted]	[redacted]	[redacted]
14	18	Ceclor	Lilly
15	7	Inderal	Ayerst
16	23	Capoten	Squibb
17	22	Halcion	Upjohn
18	34	Vasotec	MSD
19	11	Ortho-Novum	Ortho
20	40	Proventil	Schering
21	13	Lasix	Hoechst
22	15	Darvocet-N	Lilly
23	25	Procardia	Pfizer
24	21	Theo-Dur	Key
25	28	Ortho-Novum 7/7/7	Ortho
26	24	Lopressor	Geigy
27	16	Motrin	Upjohn
28	48	Ventolin	Allen & Hanburys
29	27	Dilantin	Parke Davis
30	29	Monistat	Ortho
31	32	Feldene	Pfizer
32	60	Calan	Searle
33	19	Valium	Roche
34	36	Micro-K	Robins
35	30	Slow-K	CIBA
36	50	Augmentin	Beecham
37	56	Micronase	Upjohn
38	35	Alupent	Boehringer
39	33	Lo/Ovral	Wyeth
40	31	Maxzide	Lederle
41	37	E-Mycin	Upjohn
42	52	Provera	Upjohn
43	57	Flexeril	MSD
44	44	Clinoril	MSD
45	54	APAP w/Codeine	Rugby
46	43	Minipress	Pfizer
47	41	Hydrochlorothiazide	Rugby
48	51	Triphasil	Wyeth
49	38	E.E.S.	Abbott
50	130	Retin-A	Ortho
51	47	ERYC	Parke Davis
52	76	Carafate	Marion
53	49	Timoptic	MSD
54	59	Coumadin	Du Pont
55	42	Ativan	Wyeth
56	198	Hydroxyzine	Rugby
57	66	Vicodin	Knoll
58	61	Nitrostat	Parke Davis
59	53	Transderm-Nitro	CIBA
60	77	Furosemide	Rugby
61	87	DiaBeta	Hoechst
62	86	Glucotrol	Roerig
63	70	Amoxicillin	Warner Chilcott
64	58	Corgard	Princeton
65	64	Dipyridamole	Rugby
66	97	Ibuprofen	Rugby
67	96	Anaprox DS	Syntex
68	63	Persantine	Boehringer
69	71	Entex LA	Norwich
70	*	Mevacor	MSD
71	26	Keflex	Dista
72	69	Moduretic	MSD
73	45	Tranxene	Abbott
74	145	Lopid	Parke Davis
75	102	Tavist-D	Sandoz
76	147	Zovirax	Burroughs
77	113	Beepen VK	Beecham
78	89	Duricef	Mead Johnson
79	95	Pen Vee K	Wyeth
80	104	Trental	Hoechst
81	74	Thyroid	USV
82	93	Tegretol	Geigy
83	72	Isordil	Wyeth
84	46	Aldomet	MSD
85	118	Lotrisone	Schering
86	81	K-Tab	Abbott
87	85	Penicillin VK	Warner Chilcott
88	78	Demulen	Searle
89	82	Nicorette	Lakeside
90	127	PCE	Abbott
91	62	Norinyl	Syntex
92	90	Percocet-5	Du Pont
93	190	Phenergan	Wyeth
94	101	Omnipen	Wyeth
95	92	Prednisone	Rugby
96	94	Macrodantin	Norwich
97	98	Fiorinal w/Codeine	Sandoz
98	185	Estraderm	CIBA
99	67	Indocin	MSD
100	79	Restoril	Sandoz

(continued)

EXHIBIT 2.

IMSPACT SPECIAL REPORT
THYROID AND ANTI-THYROID MARKET

Total Dollars, Drugstore and Hospital Dollars Units, and Trending

1988

Prepared For:

Dr. Bernard Wilson

DANIELS PHARMACEUTICALS

March 17, 1989

IMS-IMSPACT
DAN

THYROID AND ANTI-THYROID MARKET
1988

PAGE 1
02/15/89

-------------------------------------YEAR/DEC/88-------------------------------------

	DOL/TOT $000's	+	UN/TOT	DOL/DRG	+	UN/DRG	DOL/HOS	+	UN/HOS
[redacted]	[redacted]		9622.4	128071	+ 30	8971.9	7917	- 0	650.5
[redacted] [redacted]	[redacted]		5008.8	86323	+ 28	4740.7	4418	- 4	268.1
TABS .1MG 1000 1070-06	20908	+ 31	257.0	20676	+ 31	252.8	232	+ 23	4.3
TABS .15MG 100 1080-03	11560	+ 23	898.1	11333	+ 23	876.6	227	+ 24	21.5
TABS .1MG 100 1070-03	7670	+ 22	763.4	7373	+ 22	729.7	297	+ 35	33.7
TABS .2MG 1000 1140-06	7438	+ 11	63.5	7364	+ 11	62.8	74	- 3	0.7
TABS .05MG 100 1040-03	7327	+ 33	852.5	7204	+ 33	836.6	122	+ 25	15.9
TABS .2MG 100 1140-03	7295	+ 19	504.8	7122	+ 19	491.2	173	+ 16	13.6
TABS .15MG 1000 1080-06	6909	+ 28	69.6	6838	+ 28	68.8	71	+ 12	0.8
TABS .125MG 100 1130-03	5483	+ 76	472.1	5394	+ 77	463.5	89	+ 34	8.6
TABS .3MG 100 1170-03	3202	+ 13	165.3	3146	+ 14	162.1	56	- 15	3.2
TABS .025MG 100 1020-03	2943	+ 38	378.5	2814	+ 39	357.7	129	+ 30	20.8
TABS .075MG 100 1050-03	2515	+ 58	267.2	2461	+ 58	259.8	53	+ 62	7.4
TABS .05MG 1000 1040-06	2082	+ 39	28.9	2047	+ 39	28.2	36	+ 55	0.7
VIAL 200MCG 10CC 1 1014-	1719	- 23	58.6	113	+ 13	3.4	1607	- 26	55.2
VIAL 500MCG 10CC 1 1012-	657	- 11	19.5	37	- 51	1.0	620	- 7	18.5
TABS .3MG 1000 1170-06	492	+ 1	3.7	484	+ 1	3.7	8	- 30	0.1
TABS .1MG 100UD 1070-1	351	+ 14	36.6	101	+ 3	9.6	250	+ 19	27.0
TABS .025MG 1000 1020-06	296	+ 41	4.9	282	+ 43	4.7	15	+ 14	0.2
TABS .15MG 100UD 1080-1	148	+ 10	12.1	44	+ 14	3.5	104	+ 8	8.6
TABS .125MG 1000 1130-06	140	+ 47	1.4	132	+ 50	1.3	8	+ 3	0.1
TABS .175MG 100 #1100-03	128	******	8.8	126	******	8.7	1	******	0.1
THYROID 0100 RCH	15012	+ 0	1585.5	14703	+ 0	1528.6	309	- 3	56.9
TABS 3GR 100 3555-06	3447	+ 14	312.3	3388	+ 14	304.7	60	- 0	7.6
TABS 2GR 100 3550-06	2923	+ 9	422.4	2879	+ 9	412.9	45	- 7	9.4
TABS 1GR 1000 3532-02	2476	+ 6	74.6	2450	+ 6	73.8	26	- 2	0.8
TABS 1GR 100 3532-06	1399	+ 13	369.0	1364	+ 13	356.0	35	+ 4	13.0
TABS 2GR 1000 3550-02	853	- 2	14.5	842	- 2	14.3	11	- 8	0.2
TABS 1/2GR 100 3520-06	649	+ 9	190.0	639	+ 9	186.0	10	+ 12	4.0
TABS 4GR 100 3556-06	543	+ 8	33.1	532	+ 7	32.2	12	+ 44	0.9
TABS 3GR 1000 3555-02	478	- 7	4.7	470	- 8	4.6	8	+ 41	0.1
TABS 5GR 100 3560-06	453	+ 1	22.1	445	+ 2	21.6	8	- 28	0.5
TABS 1GR 5000 3532-03	439	- 24	3.3	437	- 24	3.2	2	- 48	0.0
TABS 11/2GR 100 3540-06	386	+ 17	64.5	379	+ 18	63.1	7	+ 7	1.4
TABS 1/2GR 1000 3520-02	332	- 2	11.4	328	- 3	11.3	4	+ 17	0.1
TABS 2GR 2500 3550-04	156	+224	1.6	154	+226	1.5	1	+ 86	0.0
TABS 1/4GR 100 3510-06	151	+ 5	48.0	148	+ 6	46.8	3	- 35	1.2
TABS 1GR 50000 3532-5	74	- 93	0.1	74	- 93	0.1	0	******	0.0
TABS 1GR ARMRDS 100UD	62	+ 4	13.3	18	+184	2.5	43	- 18	10.8
TABS 2GR ARMRDS 100UD	33	- 6	5.5	14	+ 1	1.5	19	- 11	3.9
TABS 1/4GR 1000	30	- 13	1.1	30	- 13	1.1	1	- 21	0.0
TABS 1/2GR ARMDS 100UD	23	+ 88	4.0	9	+238	1.4	13	+ 42	2.6
TABS 1/2GR 5000 3520-03	5	- 84	0.1	4	- 61	0.0	1	+ 22	0.0
THYROLAR 0170 RCH	8783	- 2	390.8	8561	- 2	378.7	222	- 1	12.1
TABS 1GR 100 0674-01	3367	+ 15	165.7	3287	+ 15	161.2	81	+ 15	4.5
TABS 2GR 100 0675-01	3169	+ 2	133.1	3097	+ 2	129.8	72	- 0	3.3
TABS 3GR 100 3630-06	1968	+ 5	68.1	1914	+ 6	65.9	54	+ 1	2.1
TABS 1/2GR 100 2605-06	311	- 67	13.1	304	- 67	12.6	7	- 66	0.5

EXHIBIT 3.

SYNTHROID PRICE INCREASES

PER MEDI-SPAN

25 mcg 100 ct		25 mcg 1000 ct		25 mcg UNIT DOSE	
02/01/81	2.40	08/01/80	19.88		
08/24/81	2.88	02/01/81	20.40		
04/30/82	3.19	08/24/81	24.44		
04/01/83	3.64	04/30/82	26.88		
12/15/83	4.19	04/01/83	30.64		
06/15/84	4.85	12/15/83	35.60		
04/08/85	5.58	06/15/84	41.23		
12/12/85	6.45	04/08/85	47.41		
11/01/86	7.11	12/12/85	54.71		
07/08/87	8.04	11/01/86	60.35		
03/31/88	9.11	07/08/87	68.21		
02/01/89	10.31	03/31/88	77.29		
		02/01/89	87.44		

50 mcg 100 ct		50 mcg 1000 ct		50 mcg UNIT DOSE	
02/02/80	2.54	08/01/80	21.62	08/01/80	2.72
02/01/81	2.70	02/01/81	22.98	02/01/80	2.88
08/24/81	3.24	08/24/81	27.53	02/01/81	3.45
04/30/82	3.56	04/30/82	30.38	04/30/82	3.81
04/01/83	4.06	04/01/83	34.63	04/01/83	4.35
12/15/83	4.69	12/15/83	39.85	12/15/83	5.06
06/15/84	5.43	06/15/84	46.11	06/15/84	5.86
04/08/85	6.24	04/08/85	53.03	04/08/85	6.74
12/12/85	7.21	12/12/85	61.20	12/12/85	7.79
11/01/86	7.95	11/01/86	67.50	11/01/86	8.59
07/08/87	8.99	07/08/87	76.30	07/08/87	9.71
03/31/88	10.19	03/31/88	86.45	03/31/88	11.00
02/01/89	11.56	02/01/89	97.81	02/01/89	12.44

75 mcg 100 ct		75 mcg 1000 ct		75 mcg UNIT DOSE	
04/01/83	4.49	04/01/83	38.19	12/15/83	5.64
12/15/83	5.23	12/15/83	44.41	06/15/84	6.54
06/15/84	6.05	06/15/84	51.43	04/08/85	7.52
04/08/85	6.96	04/08/85	59.14	12/12/85	8.69
12/12/85	8.04	12/12/85	68.26	11/01/86	9.59
11/01/86	8.86	11/01/86	75.29	07/08/87	10.84
07/08/87	10.01	07/08/87	85.10	03/31/88	12.28
03/31/88	11.35	03/31/88	96.41	02/01/89	13.88
02/01/89	12.88	02/01/89	109.06		

100 mcg 100 ct	
02/02/80	2.68
02/01/81	3.06
08/24/81	3.66
04/30/82	4.06
04/01/83	4.64
12/15/83	5.39
06/15/84	6.24
04/08/85	7.17
12/12/85	8.28
11/01/86	9.13
07/08/87	10.31
03/31/88	11.69
02/01/89	13.25

100 mcg 1000 ct	
02/02/80	22.75
02/01/81	26.04
08/24/81	31.20
04/30/82	34.31
04/01/83	39.11
12/15/83	45.80
06/15/84	53.03
04/08/85	60.98
12/12/85	70.38
11/01/86	77.63
07/08/87	87.74
03/31/88	99.41
02/01/89	112.44

100 mcg UNIT DOSE	
02/02/80	2.88
02/01/81	3.36
08/24/81	4.03
04/30/82	4.44
04/01/83	5.06
12/15/83	5.81
06/15/84	6.74
04/08/85	7.75
12/12/85	8.94
11/01/86	9.86
07/08/87	11.15
03/31/88	12.64
02/01/89	14.31

112 mcg 100 CT	
02/01/89	15.38

112 MCG 1000 CT	
02/01/89	130.50

112 mcg UNIT DOSE	
02/01/89	16.63

125 mcg 100 ct	
04/01/83	5.49
12/15/83	6.28
06/15/84	7.26
04/08/85	8.35
12/12/85	9.65
11/01/86	10.65
07/08/87	12.04
03/31/88	13.64
02/01/89	15.44

125 mcg 1000ct	
04/01/83	46.68
12/15/83	53.34
06/15/84	61.74
04/08/85	71.00
12/12/85	81.94
11/01/86	90.38
07/08/87	102.15
03/31/88	115.74
02/01/89	130.88

125 mcg UNIT DOSE	
02/01/89	16.69

150 mcg 100 ct	
02/02/80	3.22
02/01/81	3.72
08/24/81	4.46
04/30/82	4.94
04/01/83	5.63
12/15/83	6.48
06/15/84	7.49
04/08/85	8.61
12/12/85	9.94
11/01/86	10.96
07/08/87	12.39
03/31/88	14.04
02/01/89	15.88

150 mcg 1000 ct	
10/01/80	37.88
04/30/82	41.69
04/01/83	47.53
12/15/83	55.04
06/15/84	63.65
04/08/85	73.20
12/12/85	84.48
11/01/86	93.18
07/08/87	105.31
02/01/89	134.94

150 mcg UNIT DOSE	
02/01/89	17.19

175 mcg 100 ct	
02/01/89	19.00

175 mcg 1000 ct

175 mcg UNIT DOSE

200 mcg 100 ct

02/01/80	4.38
08/24/81	5.25
04/30/82	5.81
04/01/83	6.93
12/15/83	7.76
06/15/84	8.98
04/08/85	10.32
12/12/85	11.91
11/01/86	13.15
07/08/87	14.86
03/31/88	16.84
02/01/89	19.06

200 mcg 1000 ct

02/02/80	30.72
02/01/81	37.20
08/24/81	44.56
04/30/82	50.44
04/01/83	57.50
12/15/83	65.99
06/15/84	76.29
04/08/85	87.73
12/12/85	101.25
11/01/86	111.68
07/08/87	126.23
03/31/88	143.01
02/01/89	161.69

200 mcg UNIT DOSE

08/01/80	3.67
02/01/81	4.74
08/24/81	5.68
04/30/82	6.25
04/01/83	7.13
12/15/83	8.39
06/15/84	9.69
04/08/84	11.14
12/12/85	12.86
11/11/86	14.19
07/08/87	16.04
03/01/88	18.18
02/01/89	20.56

300 mcg 100 ct

02/02/80	5.42
02/01/81	6.00
08/24/81	7.19
04/30/82	7.94
04/01/83	9.05
12/15/84	10.48
06/15/84	12.13
04/08/85	13.94
12/12/85	16.10
11/01/86	17.76
07/08/87	20.08
03/31/88	22.75
02/01/89	25.75

300 mcg 1000 ct

02/02/80	46.11
02/01/81	51.00
08/24/81	61.10
04/30/82	67.25
04/01/83	76.66
12/15/83	89.04
06/15/84	103.06
04/08/85	118.52
12/12/85	136.78
11/01/86	150.46
07/08/87	170.53
03/31/88	193.20
02/01/89	218.44

300 mcg UNIT DOSE

08/01/80	5.20
02/01/81	6.42
08/24/81	7.69
04/30/82	8.50
04/01/83	9.68
12/15/83	11.31
06/15/84	13.10
04/08/85	15.07
12/12/85	17.40
11/01/86	19.19
07/08/87	21.69
03/31/88	25.58
02/01/89	27.81

200 mcg INJECTABLE

10/01/80	16.20
04/30/82	17.75
04/01/83	19.88
12/15/83	22.86
06/15/84	29.98
04/08/85	32.08
12/12/85	33.68
11/01/86	36.78
07/08/87	40.10

500 mcg INJECTABLE

08/01/80	16.79
02/01/81	20.34
04/30/82	22.25
04/01/83	24.93
12/15/83	28.66
06/15/84	32.96
04/08/85	35.27
12/12/85	37.04
11/01/86	40.45
07/08/87	44.10

EXHIBIT

WALLACE WERBLE, SR., FOUNDER

Founded 1939 — $450 a year

F-D-C REPORTS
TRADEMARKS REG. U.S. PATENT OFFICE

"The Pink Sheet"

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BOOTS IS NO *SKIN-FLINT* WHEN IT COMES TO EXPANDING FIRM's U.S. Rx SALES PRESENCE; U.K. FIRM OFFERS 9 TIMES 1985 SALES FOR BAXTER's FLINT LABS

Boots is paying a top premium of about nine times sales for Flint Labs to protect its ability in the future to "derive full benefit from the sales of its products rather than ceding a large part of the profit from products to licensees."

The British company candidly explained its willingness to bid way above the going rates to purchase Baxter Travenol's retail drug business. Without directly mentioning the ibuprofen experience, the company indicated its view of the sales it lost by letting Upjohn develop the U.S. tradename for the chemical.

An expanded self-marketing effort in the U.S., Boots said, will create trademarks to lengthen product life-cycles. "By launching and marketing products in its own name," Boots said, the company "will enjoy the benefit of the goodwill associated with its products after the expiry of their patent lives."

Boots has been forced to participate as a contract manufacturer and compete with generics on a price basis in the U.S. ibuprofen market. Upjohn, by contrast, did $120 mil. in sales with its ***Motrin*** brand in the face of generic competition in 1985. Indicative of Boots' relegation to the ibuprofen generic market, the company received two ANDA approvals in late July for the 800 mg. dosage of ibuprofen, one under its ***Rufen*** tradename and one without a tradename — presumably to supply other generic marketers.

Flint Has Wrung Big Profits Out Of Off-Patent Product *Synthroid*: Over-60% Pretax Margin In 1985

► The Flint acquisition will build Boots' U.S. sales force from about 190 to 240-250, Boots said. In an Aug. 6 release announcing the purchase, Boots said Flint "will provide a substantial increase in Boots U.S. pharmaceutical sales and its prospects." The British firm says it plans no reductions in Flint staff.

The acquisition appears primarily as a long-term move to build on Boots' eight-year experience in the U.S. market. However, Boots declared that it expects short-term results.

"Rationalization in the overheads and sales forces of the two businesses and wider marketing will be achieved at an early stage, so that the combined operation will produce significantly greater overall sales and increase the profit potential of existing products," the company said. Boots added that "this will partly be achieved because sales representatives of both businesses concentrate on visiting family doctors, and the combined sales force will be able to handle each other's product range."

BOOTS/FLINT COMBINED 1985 SALES

Boots U.S.	$82 mil.
Flint Labs	$54 mil.
Chymopapain (worldwide)	$10-15 mil.

According to the figures released on Flint, the Baxter subsidiary has an outstanding profit level. In 1985 Flint had pretax earnings of $33.1 mil., which was 61.6% of sales totaling $53.7 mil. Boots noted that "the combined sales of pharmaceutical products in the U.S. of the Boots Group and Flint would have totalled $136 mil." in calendar 1985. Boots had 1985 U.S. sales of approximately $82 mil.

Flint has maintained its profits while basing its business on an off-patent product, *Synthroid* (levothyroxine) for the treatment of thyroid deficiency. The product accounted for 83% of Flint's 1985 sales (not including the chymopapain products), or $44.3 mil. Boots noted that although Synthroid has been off patent for several years, it held 74% of the U.S. synthetic thyroid replacement market in 1985 and 57% of the total U.S. thyroid replacement market. Levothyroxine is viewed as one of the most difficult drug products to replicate with the same levels.

Flint also markets *Choloxin* (dextrothyroxine) for reduction of cholesterol and two products for treatment of burns and wounds, *Flint SSD* (silver sulfadiazine) and *Travase* (sutilains ointment). Boots is also getting the herniated disc product, chymopapain *[Chymodiactin/Discase]*. The way was paved for the inclusion of chymopapain in the deal when Baxter acquired rights to Smith Labs' Chymodiactin brand in July ("The Pink Sheet" July 28, T&G-6). At that time, Baxter estimated that the world market for chymopapain is $10-15 mil. annually.

Boots noted that the active ingredients in Synthroid and Choloxin are manufactured by Flint in Kingstree, South Carolina, and Cleveland, Mississippi and tableted in Jayuya, Puerto Rico, in facilities leased with various parties and shared with other divisions of Baxter Travenol. Flint's other products are manufactured under contract by third parties.

Flint's lack of facilities is not a negative for Boots. The British firm recently opened a $36 mil. production, warehousing and laboratory facility in Shreveport, Louisiana. The company also has facilities in Palisades Park, N.J. Prior to the Flint purchase, but with the new facility, Boots was in the position of having a pipeline of products from overseas, the necessary manufacturing facilities, but a weak marketing structure. Boots was rumored to have offered Revlon more than the $700 mil. that Rorer paid to purchase USV and Armour.

When Boots purchased its first toehold in the U.S. market through the acquisition of Rucker Pharmacal in 1977, it inherited a manufacturing facility with a number of production problems. During a 1983 inspection by FDA, the company received a report from the FDA investigator with 30 alleged deficiencies. The new plant was recently inspected for production of an ibuprofen line extension and showed only one deficiency relating to the misrecording of a tablet punch die process.

Boots said it believes the "combined enterprise" of its existing operations with Flint "will have the cash flow and sales force upon which to build the scale of operation required to market new products in the U.S." The British firm said its U.S. subsidiary "is not yet big enough to handle the launch of major new products on its own."

With Flint, Boots plans to launch the antidepressant *Prothiaden* (dothiepin). That drug had been under license to Marion, which had been developing it for U.S. marketing until earlier this summer. When Boots repurchased rights to the product ("The Pink Sheet" June 9, In Brief).

Boots also recently traded for rights to the erythromycin brand *E-Mycin* giving Upjohn exclusive marketing rights on the NSAID, flurbiprofen (Upjohn's *Ansaid*). Boots kept topical ophthalmic rights to the drug.

Other products in Boots' pipeline include flosequinan (BTS 49465), an arteriovenous vasodilator that Boots said is in *Phase II* clinicals for hypertension in the U.S., U.K. and other European countries. Boots noted that the drug has demonstrated "potential in the treatment of heart failure." The firm also has an antidepressant, BTS 54524, in clinicals. Another product, *Furamide* (diloxamide fuorate), is under investigation for the orphan indication of asymptomatic intestinal amebiasis.

Boots' current product line includes Rufen; *Lopurin* (allopurinol); *Zorprin* (zero-order release aspirin); *Ru-Tuss* Rx tablets and capsules and OTC Ru-Tuss expectorant and liquid; the topical corticosteroid *F-E-P Creme;* and the potassium agents *Twin-K* and *Twin-K-Cl.* In June, the firm also licensed the bulk laxative *Konsyl* from LaFayette with the option to buy.

Boots is purchasing Flint for $555 mil. in cash "plus a royalty based on future sales [of Flint products] once these are in excess of current expectations," Boots stated. To finance the acquisition, Boots is selling 184 mil. common shares "conditionally placed through the market at £2.05 per share." Under an agreement with Boots, investment banker Morgan Grenfell & Co. is purchasing or procuring purchasers for all the new common Boots shares. The acquisition is expected to be completed on Sept. 3.

By comparison, Boots paid $25 mil. in 1977 for Rucker Pharmacal. The figure represented 16 times Rucker's 1976 net earnings of $1.5 mil. Rucker, a regional branded generic firm, had 80 detailmen at the time of the purchase.

The Flint deal is a boon for Baxter Travenol. The company has gained almost $1 bil. from the divestitures of Flint and American Critical Care. DuPont paid $425 mil. for American Critical Care, approximately eight times 1985 sales of approximately $50-55 mil. and in the range of 30 times earnings ("The Pink Sheet" July 14, p. 3). Baxter announced its intent to sell the two pharmaceutical units in April as part of a strategy following its merger with American Hospital Supply Corp.

> **"The acquisition of Flint which has been under consideration for some time but has only recently become available, will substantially increase Boots' presence in the U.S. market and represents a major strategic step for Boots in developing its U.S. pharmaceutical business."**
>
> — August 6 press release

Baxter said its debt will be down to 35% of total capital after the sale of Flint. The company's debt was at 47% when it purchased American Hospital Supply.

AKZO PURCHASES TWO U.S. GENERIC DRUG FIRMS, PHARMACEUTICAL BASICS AND COLMED LABS; DUTCH FIRM WILL BEGIN MARKETING GENERICS IN U.S.

Akzo is entering the U.S. generic drug business with three "exclusive" generic products: amantadine, clofibrate, and carbamazepine. Akzo obtained the three products through the July 1 acquisitions of Colmed Labs and Pharmaceutical Basics. Akzo is combining the two Colorado generic companies into a new company, operating under the name VPF.

Colmed received approval for carbamazepine 200 mg tabs (Ciba-Geigy's *Tegretol*) on May 15. Approval for clofibrate (Ayerst's *Atromid-S*) was obtained by Colmed's Formutec division on June 16. The Formutec division subsequently received approval for amantadine (Du Pont's *Symmetrel*) August 5. Formutec was a division of Colmed established to handle soft elastic gelatin formulations.

Pharmaceutical Basics will manufacture carbamazepine and market all three of the new generics for Akzo. Clofibrate and amantadine, however, will be manufactured and co-marketed by Chase Labs under an agreement with Colmed ("The Pink Sheet" Aug. 4, T&G-2). Pharmaceutical Basics produces only tablet and hard capsule dosage forms. [More]

WSJ 8/7/86

EXHIBIT 5.

INTERNATIONAL

Boots Co. Agrees to Acquire Drug Unit Of Baxter Travenol to Boost U.S. Sales

By Paul Hemp

Staff Reporter of The Wall Street Journal

LONDON—Boots Co. said it agreed to acquire the Flint prescription-drug unit of Baxter Travenol Laboratories Inc. for at least $565 million with the aim of boosting its direct sales in the U.S. prescription-drug market.

The British pharmaceutical concern conceded it was paying Baxter Travenol, a Deerfield, Ill., medical-products concern, a high price for Flint, which reported 1985 pre-tax profit of $33.1 million on sales of $53.7 million and which has tangible assets of only about $13 million.

But the company said the price was justified by Flint's high profit margins and the difficulty in finding suitable drug companies to use as a base for a major assault on the U.S. market.

Available U.S. pharmaceutical businesses "are scarce and the competition for them is fierce," said Robert Gunn, Boots's chairman.

Paying a Premium

However, some analysts said Boots was paying a premium price for an essentially one-product business in a mature market; 83% of Flint's sales come from a drug, no longer under patent, to treat thyroid deficiency that Boots officials say has little sales potential outside the U.S. "They're certainly not buying Flint for its products," said Peter Woods, an analyst at De Zoete & Bevan, a London stockbrokerage. "There's little market potential there."

Boots's businesses include a chain of retail drugstores and the manufacture and marketing of pharmaceuticals and consumer products.

A U.S. pharmaceutical division manufactures and sells Boots products. But in the U.S., Boots mainly has operated by licensing other companies to make and market its prescription drugs. For example, Upjohn Co. sells Boots's Motrin, one of the best-selling drugs in the U.S. for the treatment of rheumatism.

Boots said it plans to finance the acquisition by selling about 184 million new shares, valued at $3.04 each, to raise $559 million. The company currently has about 735 million shares outstanding.

Flint's sale completes Baxter Travenol's plan to withdraw from pharmaceuticals to concentrate on its hospital-supply and remaining businesses. Last month the company announced an agreement to sell its critical-care drug unit to Du Pont Co. for $425 million. In May the company completed the $165 million sale of its American Medical Optics unit to a SmithKline Beckman Corp. unit.

Market Expectations

On the London Stock Exchange yesterday, Boots fell 13 cents, to $3.16. Its stock has been weak recently because of market expectations that the company would issue a large number of new shares.

Company officials noted that Boots has several drugs under development that it hopes to bring to market in the next few years. A U.S. sales force will help the company realize a greater share of the profits from new products, contrasted with its current licensing approach.

For example, Boots said Upjohn realized profits of $38.2 million on 1981 Motrin sales of $191 million, while Boots only made $13.2 million in royalties and other income from Motrin.

Boots says it needs a stronger base in the U.S., which accounts for 28% of the world drug market, to launch and market new products there. The company posted U.S. sales of $81 million in 1985.

Boots, which reported net income of $201.4 million on sales of $3.15 billion for the year ended March 31, has recently been the subject of takeover rumors. But company officials said the Flint acquisition wasn't meant to thwart a takeover and had been contemplated for some time.

Boots said the sale of new shares is the largest so-called vendor placing ever in London. Under the placing, Boots plans to issue to Baxter Travenol new shares that Boots's merchant bank, Morgan Grenfell & Co., will then purchase and sell to institutional investors. Those sales are conditional, though, as Boots shareholders have the right to buy all the shares back from the investors at the $3.04-a-share sale price.

1/11/90 813·323·5151
Bernard Wolfson, PhD. "call me Bernie"

- Levothyroxine sodium + Liothyronine sodium
  has an NDA and ANDA.
  A combination drug, unlike Levothyroxine Sodium.

- Levothyroxine sodium is a Pre-38 drug.
  - Daniels · Levoxine
  - Rorer · Levothroid
  - Boots · Synthroid
  - Also some "generics" out there (had hx of bioequiv. probs)
- How know these 3 are equivalent?
  - Daniels ran a study showing bioequivalence
    = Rorer's + Boots products.
    Published in Drug Intelligence + Clinical Pharmacy.
  - He has a letter from FDA saying that
    the product is allowed to be grandfathered.
  - Not based on clinical trials, but FDA
    did say the Levoxine product is "identical".

- Boots has the lion's share of the market
  80-85% of the total $120 Mn market.

- Rorer has never gone after Boots market share,
  inexplicably. Even in early 1980's when there
  was a severe quality problem (under-potency)
  (FDA let the ~~Boots~~/Flint people reformulate)

- "No R+D went into Synthroid".
  Very little went into Levoxine, too.

J. JAMES EXON
NEBRASKA

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Lincoln, NE 68508

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Omaha, NE 68102

276 Federal Building
North Platte, NE 69101

2106 First Avenue
Scottsbluff, NE 69361

[illegible]

United States Senate
WASHINGTON, DC 20510-2702

COMMITTEES:
ARMED SERVICES
COMMERCE, SCIENCE, AND TRANSPORTATION
BUDGET

90

December 26, 1989

The Honorable David Pryor
Chairman
Special Committee on Aging
United States Senate
Washington, D.C. 20510

Dear David:

I was extremely pleased to see that you have begun a series of hearings focusing on the pharmaceutical industry. I have long been concerned with many of the questions you are raising in your hearings.

I am forwarding to you a letter from one of my constituents, Don Arnold, R. P., President-elect of the Nebraska Pharmacists Association. He makes some valid points and I want to ensure that his concerns were made a part of the official record of your hearings.

Again, David, thank you for holding these very important hearings. I will look forward to reading the findings and suggestions you have at the end of the process.

With warm personal regards.

Sincerely,

Jim Exon
United States Senator

Enclosure

Dec. 9, 1989

Dear Sen. Exon,

I wish to express to you my views on two subjects that concern pharmacy and that concern my patients equally as well.

The first is discriminatory pricing by the drug manufacturers. I have read where Sen. Kerry does not feel that this is a problem. I beg to differ with him! A company such as Smith, Kline, & French makes a product called Dyazide at a cost of approximately $9.00! They sell it to me through the wholesalers at a cost of $304.67. They sell it to the hospital buying groups for $50 to $75. I believe it is highly unfair for me to have to charge my patients excessive prices when we should beable to purchase this for the same price that they extend to "non-profit" hospitals. This would be a tremedous savings for the elderly and others that have to take a medication such as Dyazide.

The second point I would like to make, is the excessive price increases that the brand-name manufacturer's have been passing down to the wholesalers and to the pharmacies. The national inflation rate is between 6 to 7% and yet the inflation rate on brand drug products has been running around 14% per year. This is excessive pricing and it is taking advantage of the elderly who take the greatest share of the medications. We all understand that the costs of materials goes up each year,but not at this rate!

I am asking you to consider these points because too many people have turned their faces and looked the other way while our drug manufacturer's have been getting richer & richer! It is not fair to the American people!

I thank you for your attention to this matter!

Respectfully yours,

D. C. Arnold

Don C. Arnold R.P.
President-Elect
Nebraska Pharmacists Association

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HEALTH
GROUP

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Joseph Sonnabend, M.D.
Richard Whitfield

Aging

20 JAN

4 January 1990

Senator David Pryor
Chairman, US Senate Special
  Committee on Aging
Russell Senate Office Building
Washington, DC 20510-0402

Dear Senator Pryor:

I write in response to a letter dated 29 November 1989 that was sent to you by Brian Tambi of Lyphomed, Inc. Mr. Tambi wrote to reply to my testimony at the Senate Special Committee on Aging hearings on prescription drug pricing that you chaired in November, 1989. I understand that Lyphomed officials declined an invitation to appear at these hearings.

Mr. Tambi erroneously characterizes the People With AIDS Health Group's project to assist PWAs (people with AIDS) in importing personal use quantities of pentamidine from England as "illegal." The Food and Drug Administration has a longstanding policy of permitting medications to be imported by individuals under certain circumstances. Specifically, individuals are permitted to import medication provided that 1) the medicine is for personal use, 2) the quantity does not exceed a three month supply, and 3) the individual is under the care of a licensed physician in the United States. The PWA Health Group goes to considerable lengths to help individuals comply with these guidelines and I have gone on record many, many times to reiterate our agency's intention to do so. Although Lyphomed has petitioned the Food and Drug Administration repeatedly to issue a directive curtailing personal use imports of pentamidine, the agency has wisely declined to do so.

Mr. Tambi also contends that the pentamidine imported by individuals may be unsterile, or may in fact be an unfinished product. Neither of these allegations is true of the pentamidine imported by individuals with the assistance of the PWA Health Group. Rather, the pentamidine imported with the assistance of the Health Group is precisely the same pharmaceutical product that had been imported by the Centers for Disease Control for many years, and complies fully with the standards outlined in the FDA's personal use importation guidelines.

On a technical note, I should like to point out that PWAs often refer colloquially to the device used for the administration of aerosol pentamidine as a "nebulizer." In fact, the entire assembly consists of an air compressor and a disposable plastic *nebulizer system*, consisting of a connecting tube, plastic mouthpiece and filter. The Respirgard II *nebulizer system*, which must be completely replaced after each use, is the only one FDA approved for the administration of aerosolized pentamidine, but there are other models in use. While the retail price of the Respirgard II is around $8, as Mr. Tambi states, he neglects to mention that the device will not operate without the air compressor. Compressors vary considerably in price, but often run hundreds of dollars.

Finally, Mr. Tambi evades the very issue that drives our clients to import pentamidine, a drug that is recognized as safe and effective in this country: the price. Certainly, he cannot deny that the price of pentamidine in this country is markedly higher than it is in England, nor has he been able to adequately explain the differential. Mr. Tambi may know AIDS activists who have received a satisfactory explanation of Lyphomed's pricing strategies for pentamidine. We do not.

The anomaly of U.S. citizens importing life-sustaining medications because they cannot afford them here has drawn substantial attention to the issue of drug pricing in the United States. We agree with Mr. Tambi's suggestion that laws regulating such a vital component of our healthcare system deserve careful consideration by Congress and we fully support congressional efforts to prevent the sort of profiteering that has driven up the price of pentamidine by nearly four hundred percent. We applaud efforts like those of your committee to better understand these issues and to help devise more equitable means of providing healthcare for all those in need.

Again, thank you for your attention to these matters. If we may be of any further assistance, or if you would care to discuss these issues in greater detail, please do not hesitate to contact me at any time.

Sincerely yours,

Derek Hodel

Derek Hodel

/dh

Pharmaceutical
Manufacturers
Association

Gerald J. Mossinghoff
PRESIDENT

January 19, 1990

The Honorable David H. Pryor
Chairman
Senate Special Committee on Aging
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

The Pharmaceutical Manufacturers Association takes strong exception to the November 16, 1989 briefing paper prepared by the majority staff of the Senate Aging Committee, which recommended the creation of a restrictive formulary for Medicaid beneficiaries. Such a restrictive formulary would be costly and counterproductive, and would relegate Medicaid beneficiaries to a system of second-class medicine.

I am enclosing, for your use and information, our response to the Aging Committee staff report, entitled "Protecting Medicaid Beneficiaries from Restrictive Formularies." Our paper makes three critical points:

- The indiscriminate exchange of one drug for another can produce adverse effects or inferior therapeutic results.

- There is a growing body of evidence that patients who are denied a full array of drug therapies often require more expensive alternative medical treatment, such as physician services, hospitalization, and surgery.

- The U.S. patent system encourages innovation by rewarding it economically. Without the economic incentives, U.S. pharmaceutical companies could lose their preeminent position in the world marketplace.

We hope you will have an opportunity to review the enclosure, which responds to the very serious misconceptions which served as the basis for the majority staff's recommendations. Please let me know if you have any questions or if we can be of further assistance.

Sincerely,

Gerald J. Mossinghoff

Enclosure

1100 Fifteenth Street NW, Washington, DC 20005 • Tel: 202-835-3420 • FAX: 202-835-3413, 3414

PROTECTING MEDICAID PATIENTS FROM RESTRICTIVE FORMULARIES

A Response to the
November 16, 1989,
Briefing Report of the
Majority Staff of the
Senate Special Committee on Aging

January 19, 1990

Pharmaceutical
Manufacturers
Association

PROTECTING MEDICAID PATIENTS FROM RESTRICTIVE FORMULARIES

EXECUTIVE SUMMARY

In a November, 1989 briefing report, the majority staff of the Senate Special Committee on Aging endorsed the use of restrictive formularies -- an outmoded and ineffective system of cost-containment -- for Medicaid's prescription drug reimbursement program. Formularies typically exclude certain drugs and categories of drugs from reimbursement, thus greatly restricting their use in preventing and treating illnesses.

The majority staff would restrict Medicaid patients to the lowest priced prescription drugs. The prices of these products would be established through negotiations between program administrators and pharmaceutical manufacturers. A drug still on patent would not be included on formularies if the patentholder declined to reduce his price. Patients instead would be switched by pharmacists to drugs deemed "therapeutically equivalent" by program administrators.

A number of states have used restrictive Medicaid formularies. Other states in recent years have moved to abolish or greatly expand their formularies, based on evidence that formularies do not save money and do more harm than good.

The majority staff's endorsement of formularies was based on three false assumptions:

1. That there are no important differences between drugs in the same therapeutic class. In fact, there is no such consensus on therapeutic equivalence. Leading physicians and pharmacists reject this notion because of individual differences among patients.

2. That restrictive drug formularies which exclude certain drugs will save the Medicaid program money. In fact, there is increasing evidence that restrictive formularies cause total Medicaid expenditures to rise rather than fall. This is because patients who are denied drug therapies often require more physician services, hospitalization and surgery.

3. That forcing companies to lower prices in order to gain access to a formulary will have no harmful effect on U.S. pharmaceutical innovation. In fact, formularies undermine patent protection, and patent protection clearly affects the rate of pharmaceutical innovation.

But the worst effect of formularies is on Medicaid patients themselves. By denying these patients the newest and often most effective therapies, formularies create a second-class system of medicine.

PROTECTING MEDICAID PATIENTS FROM RESTRICTIVE FORMULARIES

INTRODUCTION

The second briefing paper prepared by the Majority Staff of the Senate Special Committee on Aging, Skyrocketing Prescription Drug Prices: Turning a Bad Deal into a Fair Deal (November 16, 1989) ("second staff report"), continues the majority staff's attempt to evaluate the appropriateness of prescription drug pricing levels. PMA responded to the majority staff's first briefing paper, Prescription Drug Prices: Are We Getting Our Money's Worth? (July 18, 1989), with its own analysis of the facts in America's Pharmaceutical Research Companies: A Cost-Effective Source of Important New Medicines (November 15, 1989).

Like the first briefing paper, the second staff report makes preliminary "findings" based on its survey of pharmacy directors and physicians at a number of hospitals, Medicaid programs and health maintenance organizations (HMOs). Originally, the staff was concerned about the federal budget impact of forthcoming drug reimbursement by Medicare, a program of special interest to the Senate Special Committee on Aging. With Congress's recent repeal of the Medicare Catastrophic Coverage Act, Medicare no longer is scheduled to reimburse for outpatient drug purchases. Consequently, the staff's focus has shifted to Medicaid.

Taken together, the staff's "findings" suggest that pharmaceutical companies can be forced to negotiate lower prices for drugs if state Medicaid programs threaten to deny uncooperative companies the opportunity to have their products listed on Medicaid formularies. The staff asserts that even for drugs that are still on patent, Medicaid officials can stimulate price competition because there are different drugs in the same therapeutic class that can be substituted by the Medicaid program for the patented product. To deflect criticism that such a forced-negotiation policy could deny Medicaid patients needed drugs, the staff assumes that:

I. There are no important differences between drugs in the same therapeutic class;

II. Restrictive drug formularies which exclude certain drugs will save the Medicaid program money; and

III. Forcing companies to lower prices in this manner will have no harmful effect on U.S. pharmaceutical innovation.

As this paper will show, these assumptions are false.

I. ASSUMPTION: There are no important differences between drugs in the same therapeutic class.

FACT: DRUGS IN THE SAME THERAPEUTIC CLASS ARE NOT NECESSARILY INTERCHANGEABLE.

A. Consensus Does Not Exist on Therapeutic Equivalence.

The majority staff contends that "(p)hysicians and pharmacists in over 90% of the nation's hospitals and at least 42% of U.S. health maintenance organizations (HMOs) have independently concluded that many prescription drugs are therapeutically interchangeable when used to treat patients suffering from the same ailment." (Finding 3) But, in fact, there is no such consensus on therapeutic interchangeability. As John Ballin, PhD, of the American Medical Association recently wrote in the Journal of the American Medical Association:

> Despite the efforts of segments of organized pharmacy to bring about therapeutic substitution legislation, not all pharmacists embrace such practices. Many pharmacists oppose therapeutic substitution because of liability concerns. Others think that they are not competent to make the clinical judgments involved in autonomous drug selection. Still other pharmacists are concerned about alienating physicians and fear that, if there is sufficient encroachment on the physicians' prerogative, doctors will begin dispensing drugs as well as prescribing them. Thus, within the ranks of the pharmacy profession, there is wide disagreement over the desirability of this practice.
>
> There appears to be more of a consensus within the medical profession about the merits of therapeutic substitution. Not surprisingly, physicians as a group are opposed. The American Medical Association has adopted a policy of vigorous opposition to "any concept of pharmaceutical or therapeutic substitution by pharmacists." Similarly, the American Academy of Family Physicians has taken a strong position against the practice. Physicians are very concerned about potential serious consequences of therapeutic substitution on patient care, both in terms of lack of efficacy and adverse reactions. The hazards are particularly great for the elderly who may have multiple diseases, take multiple drugs, and possess very fragile biological systems." (1)

The fact that therapeutic substitutions are practiced in some hospitals and HMOs does not mean, as the staff concludes, that the physicians in those institutions favor the practice.

For example, the legislative committee of the Iowa Academy of Family Physicians has strongly recommended that Iowa physicians not sign an HMO or other managed-health-care contract that includes a therapeutic substitution clause (2).

Many pharmacists, as Dr. Ballin noted, are also uncomfortable with therapeutic substitution, particularly outside the institutional setting as would be the case with Medicaid patients' filling their prescriptions at community pharmacies. According to William A. Zellmer, editor of the American Journal of Hospital Pharmacy:

> Pharmacy must recognize, when it advocates therapeutic interchange, that the concept developed as a component of the hospital formulary system, which has long functioned effectively under voluntary practice guidelines. It would be a mistake to attempt to write therapeutic interchange into state laws for broad application in ambulatory care before there is substantial experience with the practice in that area." (3)

Indeed, state laws commonly prescribe therapeutic substitution in an outpatient setting.

B. Therapeutic Inequivalence Can Result in Adverse or Subtherapeutic Effects and Toxicity.

Different salts, esters, or dosage forms of the same active drug may differ substantially in efficacy, required dose, bioavailability, pharmacokinetic profile, or incidence of adverse effects. Substituting one drug for another may sometimes alter therapeutic effects. For example, substitution may alter plasma levels and potentially toxic clinical effects; interchange among formulations with different particle or crystal size may cause variations in absorption, leading to discrepancies in bioavailability. Substitution between different salts and esters of the same chemical could make significant differences in the proportion of active drug released into the blood stream or major differences in the effect of food on the medication's absorption (4).

Many case studies published in the medical literature describe important clinical differences between individual drugs in the same "therapeutic class." For example, William H. Frishman, M.D., of Albert Einstein College of Medicine in New

York says interchange among the nine systemic beta-blockers now marketed in the United States may result in untoward results because of differences in potency (requiring different dosages to achieve the same effect), selectivity (regarding their relative abilities to block different beta adrenergic receptors on heart muscle cells), pharmacokinetic properties (affecting their appropriateness for patients with impaired hepatic or kidney function), application to various age groups, and adverse effects (5).

Another therapeutic class that has important clinical differences among individual medicines is nonsteroidal anti-inflammatory drugs (NSAIDs), which the majority staff identifies as anti-arthritis pain medication. According to one review article, there are "up to 100 molecules now developed or in research" in the nonsalicylate NSAIDs alone (6). The committee's majority staff asserted NSAIDs have "many interchangeable drug products" (Finding 3). But highly individualistic clinical responses to different NSAIDs may occur in some arthritis patients, which may explain why chemically similar NSAIDs are not similarly effective in all patients.

The same point is made in an article in DICP, The Annals of Pharmacotherapy, by Richard A. Levy, PhD, of the National Pharmaceutical Council and Dorothy L. Smith, Pharm.D., of Consumer Health Information Corporation: "Patients are highly individualistic and the final prescribing decision must be based on therapeutic efficacy, safety, adverse reaction profile, concurrent therapy, simplicity of dosage regimen, patient acceptance and compliance, and overall cost of treatment." (7)

II. ASSUMPTION: Restrictive drug formularies, which exclude certain drugs, will save the Medicaid program money.

FACT: RESTRICTIVE FORMULARIES MAY DO MORE HARM THAN GOOD.

A. Restrictive Formularies Deny Medicaid Patients Needed Drugs or Force Them to Pay for Needed Drugs Out-of-Pocket.

Many state Medicaid formularies deny patients the best drug therapy on the market for several years after it becomes available. Between 1970 and 1980, Medicaid programs in California and Kentucky, the states with the most stringent formularies, averaged at least five years of additional delay before accepting new drugs already approved by the Food and Drug Administration. (8). Another study of six states between 1974 and 1982 showed average approval delays ranging from 11.6 months in Washington to 48.4 months for Kentucky. (9)

Medicaid patients are sometimes denied "breakthrough" drugs that could save or prolong their lives. According to the first report of the National Commission on Acquired Immune Deficiency Syndrome:

> The belief that Medicaid will pay for the health care needs of the growing number of low income people with HIV infection and AIDS is, as one expert witness told the Commission, a "Medicaid fantasy."...
>
> ... One obstacle is the wide variation among states in Medicaid eligibility and scope of benefits. The Food and Drug Administration (FDA), under considerable public pressure, has struggled with mechanisms to speed new drugs to the market. Yet there is no requirement that Medicaid make even life-prolonging drugs such as zidovudine (AZT) available. (10)

In Michigan, when 640 prescription drugs were removed from the Medicaid formulary in 1982, the program reported a 15% reduction in prescription claims. But a study by David M. Smith, a Michigan clinical pharmacist, and Patrick L. McKercher, PhD, an associate professor at Wayne State University, concluded that nearly half of the Medicaid recipients on continuous therapy had actually stopped being treated while another 30% of the recipients continued therapy at their own expense. "The out-of-pocket payment category is under-represented due to the inability of documenting costs associated with alternate OTC [over-the-counter, nonprescription] drug therapy," the authors point out. (11)

B. Evidence Suggests That Restrictive Formularies Cause Total Medicaid Expenditures To Rise Rather Than Fall.

Medicaid programs in 19 states have restricted or closed formularies, where the state will reimburse only for drug products on the approved list. Most states have a prior-authorization mechanism to allow exceptions, although few physicians seem to take advantage of it because of the "hassle factor." William J. Moore, Ph.D., and Robert J. Newman, Ph.D., of Louisiana State University's Department of Economics, conducted a PMA-supported statistical analysis of the experience of Medicaid programs in 47 states. They conclude:

> In this study we have examined the effects of state restricted formularies on the Medicaid program. While proponents argue that adoption of such regulations will reduce the drug budget and total program expenditures, our evidence suggest otherwise. Because of service substitution effects, we find that restricted formularies, by removing the method of preferred treatment, tend to increase rather than decrease the level of total Medicaid expenditures. We find no evidence to support the hypothesis that restricted formularies reduce drug expenditures. In fact, our evidence directly contradicts (in a statistical sense) claims that restrictive formularies reduce Medicaid expenditures.

As an example, Moore and Newman noted that several drug products were removed from the Louisiana state Medicaid formulary in 1976:

> Medicaid officials, at that time, estimated that the removal of these drugs would decrease the drug budget by 15.68 percent and provide a savings (reduced expenditures) to the total Medicaid program of $5.6 million... [A]ctual drug budget expenditures fell by about $3.6 million, or roughly 10.9 percent, but at the same time, total Medicaid expenditures rose by $27.1 million or approximately 14.1 percent. (12)

Other investigators have been reaching similar conclusions since the earliest studies of the impact of Medicaid formularies. In the early 1970s, Robert W. Hammel, Ph.D., of the University of Wisconsin School of Pharmacy compared Medicaid expenditures in states without a drug formulary or with an open or unrestrictive formulary with expenditures in states maintaining a closed formulary. He concluded that states with a closed formulary spent more on Medicaid on a state per capita basis than did those without a restrictive formulary. (13)

In 1982, the National Pharmaceutical Council, in cooperation with the Project HOPE Center for Health Information, sponsored a symposium and workshop on the effectiveness of medicines in containing health care costs. One of the papers presented at that conference, by Mickey C. Smith, Ph.D., of the University of Mississippi School of Pharmacy and Susan Simmons, Ph.D., of the University of Iowa College of Pharmacy explored the relationships between a variety of Medicaid cost control mechanisms, including formulary restrictions, and three dependent variables: expenditures per eligible recipient, expenditures per actual recipient, and participation rate (number of recipients compared to number of eligibles). Between 1973 and 1980, they concluded that "it would appear that formulary restrictions had little relationship to the dependent variables. Indeed, when such relationships were found, formulary limitations were often associated with higher overall drug expenditures." (14) [emphasis in original]

Most recently, Frank A. Sloan, Centennial Professor of Economics at Vanderbilt University, examined the now-extensive literature on Medicaid formulary cost savings and concluded:

> Overall, there is no evidence from the single state or the multistate studies that a restrictive Medicaid drug formulary results in savings to the Medicaid program... In Michigan, such restrictions may have placed an additional cost burden on the needy. (15)

III. ASSUMPTION: Forcing companies to lower prices of patented drugs by threatening to keep them out of state formularies if they decline to negotiate prices will have no harmful effect on U.S. pharmaceutical innovation.

FACT: DILUTING PATENT RIGHTS UNDERMINES INNOVATION.

A. The Patent System Creates A Period of Marketing Exclusivity for Valid Reasons.

Historically, the patent system in the United States has granted the innovator a limited monopoly for two reasons: 1) it encourages innovation by rewarding it economically and 2) it assures competition when the patent expires by requiring disclosure of information in the patent filing that otherwise would remain a trade secret. During the Kefauver hearings in the early 1960s, the patent protection afforded pharmaceuticals was challenged as being of less social value than the lower prices that could be expected from increased competition. The Aging Committee's majority staff is essentially making the same argument. As described by William S. Comanor of the University of California, Santa Barbara:

What is at issue here is the appropriate level of return from pharmaceutical innovation. This single question is the unifying theme for much of the policy debate that has ensnarled the pharmaceutical industry in the postwar period. The essential question is the extent to which competitive forces should be promoted or retarded so that the most desirable rate and pattern of innovation are induced. Some restrictions on competition may well promote innovation while others may not. What is therefore at issue is not merely the nature of any trade-off between competitive results and rapid innovation, but also whether one in fact exists.

In the early years of this debate, the Kefauver committee suggested that these rewards were excessive, so that patent protection accorded to new pharmaceuticals should be more limited. In recent years, as effective patent protection declined, many have taken the opposite position, and recent legislation has extended the period of patent protection. (16)

B. In Countries Where Patent Rights Are Abridged or Ignored, Innovation Suffers; Where Rights Are Expanded, Innovation Prospers.

In Canada, legislation providing for pharmaceutical compulsory licensing was enacted in 1923, although it was not until 1969 that the Canadian Parliament applied the law to drugs imported into the country as well as for those manufactured domestically. The main reason for the change was Parliament's conclusion that prices were too high and that patents were the prime reason. But the actual result was that the robust Canadian pharmaceutical R&D enterprise quickly atrophied. In 1983, the Canadian government noted that the ratio of imports to exports in the pharmaceutical field had increased several fold since 1969. Subsequent legislation, approved in November 1987, provided for a 10-year period of marketing exclusivity for pharmaceutical patentholders. The government also persuaded the pharmaceutical industry to greatly increase its R&D spending, which was a major inducement for the policy turnabout. This was an important first step, but the Canadian system of patent protection still falls short of the standards of other developed countries. (17)

In Italy, the government abolished drug patents before World War II and full patent protection for pharmaceutical inventions was not restored until 1978. During this period, the Italian pharmaceutical industry was concerned more with improving processes for molecules discovered outside Italy rather than with original research. Since 1978, the Italian pharmaceutical industry has grown significantly. Compared to a decade ago, when only one Italian company was among the world's top 100 pharmaceutical firms, now seven Italian-owned companies are among the top 100. Also, R&D investments have increased from 123.1 billion lire in 1978 to 949 billion lire in 1987, and a number of international groups have announced their decisions to establish or expand research centers in Italy. Italy now ranks fifth in the world in discovering new chemical entities used in pharmaceuticals. (18) (19) (20)

SUMMARY

The major thrust of the majority staff's second report is that pharmaceutical companies can and should be forced to negotiate the prices of their patented products with Medicaid programs to reduce the drug component of Medicaid expenditures. Companies that decline to participate in such negotiations would be denied the opportunity to have their drug products included in the Medicaid formularies. The majority staff argues that this will not hurt Medicaid patients, because therapeutically equivalent drugs can be substituted for any drugs stricken from the formulary.

However, there is no consensus that drugs in therapeutic classes such as nonsteroidal antiinflamatory drugs are equivalent. There is, in fact, widespread opposition to "therapeutic substitution" by the medical profession and also by some hospital pharmacists. And there are many examples of therapeutically inequivalent drugs in the same therapeutic classes that, if exchanged indiscriminately, can produce adverse side effects or suboptimal therapeutic results.

Evidence is accumulating that restrictive formularies themselves cause total Medicaid expenditures to rise rather than fall. When patients are denied drug therapies they often end up hospitalized or requiring surgery. Even when formularies cut program costs, they may deny patients needed therapies or require patients to pay for non-formulary drugs out-of-pocket.

If companies do agree to negotiate lower prices for drugs that are still on patent, the patent system itself will be undermined because the economic advantages of new drug discovery will be diluted. In countries where patent protection is weakened, drug innovation suffers; where drug patents are protected, innovation prospers.

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United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

January 23, 1990

Mr. Gerald J. Mossinghoff
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1100 15th Street, NW
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Dear Mr. Mossinghoff:

On behalf of the Members of the Senate Special Committee on Aging, I would like to thank you for sharing with the Committee the Pharmaceutical Manufacturers' Association's (PMA) frank and provocative report, "America's Pharmaceutical Research Companies: A Cost-Effective Source of Important New Medicines." It is clear from my review of this document that PMA has labored long and hard to put a favorable "spin" on harsh realities. After evaluating the Association's contentions, however, I have concluded that the data in PMA's report serve only to confirm three facts.

1. Most new drugs marketed by manufacturers between 1981 and 1988 had "little or no potential" at the time of their introduction to improve on treatment options already available to America's physicians. This fact emerges from Food and Drug Administration (FDA) scientists' review of manufacturers' own clinical data, and finds support in the judgement of thousands of clinicians participating in hospital and health maintenance organization pharmacy and therapeutics committees across the nation.

2. Marketing of therapeutically duplicative drugs is the norm among drug companies, whether one examines firms selected by PMA as "major" firms -- that is, those having an unusually strong commitment to research and development -- or those firms identified by the Committee staff. Specifically, Committee staff found FDA rated 84% of new drugs as offering "little or no" potential advantage over current therapies while PMA showed the same is true for 82% of the new drugs marketed by the 25 "top" manufacturers most dedicated to research and development.

3. Therapeutically duplicative drug products also account for a majority of the subgroup of new drugs known as "New Molecular Entities" (NMEs), regardless of whether one examines PMA's list of "top" companies, or the firms identified by Committee staff. Specifically, Committee staff found FDA rated 61% of NMEs as offering "little or no potential for therapeutic gain," while the same designation applies to 58% of NMEs marketed by PMA's selected group of "top" companies.

Irrespective of these data in PMA's response to the Committee staff report, PMA has argued that it is "unfair" to use FDA's "internal" drug evaluations to assess the level of innovation in the industry. I agree that it would be wrong to uncritically accept every one of FDA's judgements in this area. We examined FDA's evaluations at our July hearing because they represent a rare objective source of scientific and clinical judgement regarding the therapeutic potential of new drugs. But FDA is not alone in its assessment. In the Committee's November hearing, I learned that similar findings result from the independent deliberations of thousands of physicians and pharmacists who serve on hospital pharmacy and therapeutics ("P&T") committees across the nation.

These "P&T" committees have been established by nearly all of the nation's university teaching hospitals and community hospitals, and over 40% of the nation's largest Health Maintenance Organizations (HMOs). Because these committees meet frequently, they are in an excellent position to incorporate in their deliberations recent discoveries about new uses for old drugs. After study and debate regarding information submitted by manufacturers, review of the medical literature, and consideration of their members' own clinical experience, these committees too have found that hundreds of drug products -- including many under patent -- are safe and effective alternatives for one another.

However, it isn't just American physicians, pharmacists, hospitals and HMOs that have found so many new drugs make so little therapeutic contribution. The World Health Organization (WHO) maintains a list of "essential drugs." This WHO list is in fact one of the world's most (if not the most) conservative therapeutic formularies. This formulary of "essential drugs" is so rigorous that only ten new products have been added since 1977, with a similar number deleted. More to the point, only a handful of the several hundred new drugs introduced to the U.S. market during the 1980s even appear on WHO's "essential drug" list. WHO is yet another informed group that agrees most new drugs add little or nothing to physicians' medical treatment options.

Moreover, like the World Health Organization, U.S. hospitals and HMOs use this information to make more informed purchasing decisions. They do this by offering manufacturers an opportunity to have their product(s) listed on a therapeutic formulary, a list of preferred drug products. A therapeutic formulary allows these providers to throw the bulk of their purchasing power to the lowest bidder among several manufacturers of therapeutically equivalent products. Under this arrangement, preferred products are purchased at tremendous discounts below the manufacturer's published "Average Wholesale Price." I have learned from this that a clear-headed market valuation of "me-too" drugs is vital to a successful cost-control strategy.

I raise these issues not to embarrass the industry but to lay the groundwork for a fundamental reappraisal of the Government's cost-containment strategy for prescription drugs. These facts provide a conceptual yardstick for evaluating the claim that research and development costs justify skyrocketing drug prices. I want policymakers to be aware that while new drug prices are pegged an average of 49% above the price of drugs they replace, the FDA finds 60 to 80 percent of them offer little or no therapeutic advantage over existing products. I want my colleagues in the Congress and in the States to see what first rate health care providers have been able to do to reduce drug prices once they took off their blinders. When these facts are known, I believe Congress will authorize more Government agencies to negotiate fair prices -- instead of accepting industry's asking price -- for the high-priced "me-too" drugs on the market today.

As you can see, I am not opposed to the production of "me-too" drugs. I am simply opposed to the idea that American citizens must pay high prices for them. As a result of the Committee's hearings, and after reviewing PMA's independent confirmation of these data, I am more convinced than ever that now is the time for financially-strapped State Medicaid programs to use our knowledge of therapeutic duplication to achieve drug price discounts, the way hospitals and HMOs do. I will be introducing legislation to accomplish this goal in the second session of the 101st Congress, and invite the Association's comments on this proposal as it develops. This proposal is identified as "Option 2" in the attached pre-publication version of the second Committee staff report. Please let me know PMA's reaction to this proposal, and to the staff report itself.

Just yesterday, I received PMA's response to our second draft staff report and have not had a chance to thoroughly review it. I would say, however, that while the concerns you raise may well apply to formulary systems currently in place in some State Medicaid programs, these issues do not apply to legislation that I am considering. More thorough review of your response is underway.

Once again, thank you for your interest in the Committee's study of prescription drug prices. I look forward to working with you as discussions proceed on my legislative proposal.

Sincerely,

David Pryor
Chairman

Enclosure
DP:dgs

APPENDIX 3

JUNE 27, 1989 DRAFT REPORT TO CONGRESS, "MANUFACTURERS' PRICES AND PHARMACISTS' CHARGES"

DEPARTMENT OF HEALTH & HUMAN SERVICES

Health Care Financing Administr

The Administrator
Washington, D.C. 20201

JUN 27 1989

DRAFT

TO: The Secretary
Through: US ____
COS ____
ES ____

FROM: Acting Administrator
Health Care Financing Administration

SUBJECT: Report to Congress on Manufacturers' Prices and Pharmacists' Charges -- ACTION

Action Requested By: AS SOON AS POSSIBLE

BACKGROUND

Currently, with limited exceptions, Medicare covers outpatient drugs and biologicals that cannot be self-administered only when furnished incident to a physician's professional services or in certain other outpatient settings, and immunosuppressive drugs furnished within one year of a covered organ transplant. Sections 202 and 203 of the Medicare Catastrophic Coverage Act of 1988, Pub. L. No. 100-360 ("MCCA"), established an outpatient drug program covering catastrophic expenses for prescription drugs and insulin incurred by those persons electing Part B coverage under Medicare. Beginning on January 1, 1990, coverage includes home intravenous drugs, and extends coverage of immunosuppressive drug therapy. The program expands on January 1, 1991, to include all legend drugs, biologicals, and insulin, as now described in Section 1861(t) of the Social Security Act.

Section 1834(c)(8) of the Social Security Act, as enacted by Section 202(b)(4) of MCCA, requires that the Secretary of Health and Human Services (HHS) report to Congress on changes in manufacturers' prices and pharmacists' charges for covered outpatient drugs and on the use of covered outpatient drugs by individuals entitled to this benefit. These reports are required every 6 months in 1989 and 1990 and yearly thereafter. In response to this charge, our initial report focuses on changes in prices and charges for prescription drugs between 1981 and 1986 and examines the biannual change in prices and charges between 1987 and 1988. Also, included is a discussion on the use of covered outpatient prescription drugs by the elderly.

While the primary focus of this report is on increases in pharmaceutical prices and charges, these changes are considered in the context of factors affecting the current marketplace. The report focuses on the following considerations in relation to changes in drug pricing: (1) health and drug expenditures; (2) development and manufacture of prescription drugs; (3) single source and multiple source drug products; (4) the number of prescription drugs marketed; (5) acquisition of prescription drugs by retail pharmacies; and (6) the retail prescription dollar. The information provided describe briefly the factors influencing price and charge setting patterns for prescription drugs. This information indicates the dynamics of the pharmaceutical market as advances in drug therapy technology and improved quality in new drug products are introduced.

HIGHLIGHTS

In developing this report, we used Consumer Price Index (CPI) and Producer Price Index (PPI) data to analyze changes in manufacturers' prices and pharmacists' charges for prescription drugs. The CPI is a measure of the average change in retail prices paid by consumers for a fixed market basket of goods and services. The CPI for prescription drugs reflects retail prices for prescriptions sold through retail, community pharmacies. The PPI is designed to measure the change over time in the prices received in commercial transactions by manufacturers or producers from the sale of various goods. The CPI and PPI are tools that provide a consistent and reasonably reliable indicator of change over time in manufacturers' prices and pharmacists' charges for prescription drugs.

Highlights from the report's findings include:

- The average annual percent change in the PPI for prescription drugs between 1981 and 1986 was 10.1%. The average annual percent change in the CPI for prescription drugs during the same period was 10.2%. In contrast, the average annual percent change between 1981 and 1986 in the CPI for all items was 4.2%.

  In 1987 the PPI for prescription drugs increased 9.6% and in 1988 it rose 7.9%. In 1987 and 1988 the CPI for prescription drugs increased 8.0% and 7.8%, respectively.

- The rate of increase from 1981 - 1986 for the PPI indexes of specific therapeutic categories of drugs showed considerable differences. A number of explanations can be offered for these differences in inflation rates over time. The influence of single source and multiple source drugs and new chemical entities may provide a partial explanation of the differences in observed inflation rates across various therapeutic categories. However, not all PPI inflation can be attributed to development costs.

- The use of prescription drugs is confined to relatively few entities. The top 25 drug entities account for 28.8 percent of all drug mention: the top 500 for 88.5 percent. The drug therapy categories most commonly mentioned for the elderly during physician office visits were cardiovasculars (21.8 percent of all mentions), systemic anti-infectives (9.7 percent), diuretics (8.6 percent), analgesics (6.6 percent) and hormones (5.7 percent).

- By one report 32.2 percent of the 1986 prescription dollar went to the pharmacy, 5 percent to the wholesaler and 62.8 percent to the manufacturer.

The total estimated cost to prepare this report is $25,000.

RECOMMENDATION

I recommend you transmit the Report to Congress. Transmittal letters are attached at Tabs A and B for your signature.

DECISION

Approved ______________ Disapproved ______________ Date _____

Louis B. Hays

3 Attachments:
Tab A - Letter to the President of the Senate
Tab B - Letter to the Speaker of the House
Tab C - Report to Congress on Manufacturers' Prices and Pharmacists' Charges

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

The Honorable Dan Quayle
President of the Senate
Washington, D.C. 20510

Dear Mr. President:

I am respectfully submitting the report required by Section 1834(c)(8) of the Social Security Act, as enacted by Section 202(b)(4) of the Medicare Catastrophic Coverage Act of 1988 (MCCA; Public Law 100-360).

Currently, with limited exceptions, Medicare covers outpatient drugs and biologicals that cannot be self-administered only when furnished incident to a physician's professional services or in certain other outpatient settings, and immunosuppressive drugs furnished within one year of a covered organ transplant. Section 202 and 203 of the MCCA establishes an outpatient drug program covering catastrophic expenses for prescription drugs and insulin incurred by those persons electing Part B coverage under Medicare. Beginning on January 1, 1990, coverage includes home intravenous drugs, and extends coverage of immunosuppressive drug therapy. The program expands on January 1, 1991, to include all legend drugs, biologicals, and insulin, as now described in Section 1862(t) of the Social Security Act.

The MCCA requires that the Secretary of Health and Human Services (HHS) report to Congress on changes in manufacturers' prices and pharmacists' charges for covered outpatient drugs and on the use of covered outpatient drugs by individuals entitled to this benefit. Pursuant to this requirement, this is the first of a series of reports required of the Secretary. Reports on this same subject are to be prepared by the Secretary every 6 months during 1989 and 1990 and once a year thereafter.

The estimated cost to prepare this report is $25,000.

I am also sending a copy of this report to the Speaker of the House of Representatives.

Sincerely,

Louis W. Sullivan, M.D.
Secretary

Enclosures

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

The Honorable Thomas S. Foley
Speaker of the House of Representatives
Washington, D.C. 20515

Dear Mr. Speaker:

I am respectfully submitting the report required by Section 1834(c)(8) of the Social Security Act, as enacted by Section 202(b)(4) of the Medicare Catastrophic Coverage Act of 1988 (MCCA; Public Law 100-360).

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Sincerely,

Louis W. Sullivan, M.D.
Secretary

Enclosures

REPORT TO CONGRESS ON MANUFACTURERS' PRICES AND PHARMACISTS' CHARGES FOR OUTPATIENT DRUGS COVERED BY MEDICARE

(May 1989 Report)

Louis W. Sullivan, M.D.
Secretary
Health and Human Services
1989

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EXECUTIVE SUMMARY

Currently, with limited exceptions, Medicare covers outpatient drugs and biologicals that cannot be self-administered only when furnished incident to a physician's professional services or in certain other outpatient settings, and immunosuppressive drugs furnished within one year of a covered organ transplant. Sections 202 and 203 of the Medicare Catastrophic Coverage Act of 1988, Pub. L. No. 100-360 ("MCCA"), establishes an outpatient drug program covering catastrophic expenses for prescription drugs and insulin incurred by those persons electing Part B coverage under Medicare. Beginning on January 1, 1990, coverage includes home intravenous drugs, and extends coverage of immunosuppressive drug therapy. The program expands on January 1, 1991, to include all legend drugs, biologicals, and insulin, as now described in Section 1861(t) of the Social Security Act.

Section 1834(c)(8) of the Social Security Act, as enacted by Section 202(b)(4) of MCCA requires that the Secretary of Health and Human Services (HHS) report to Congress on changes in manufacturers' prices and pharmacists' charges for covered outpatient drugs and on the use of covered outpatient drugs by individuals entitled to this benefit. These reports are required every 6 months in 1989 and 1990 and yearly thereafter. In response to this charge, our initial report focuses on changes in prices and charges for prescription drugs between 1981 and 1986 and examines the biannual change in prices and charges between 1987 and 1988. Also, included is a discussion on the use of covered outpatient prescription drugs by the elderly.

While the primary focus of this report is on increases in pharmaceutical prices and charges, these changes are considered in the context of factors affecting the current marketplace. The report focuses on the following considerations in relation to changes in drug pricing: (1) health and drug expenditures; (2) development and manufacture of prescription drugs; (3) single source and multiple source drug products; (4) the number of prescription drugs marketed; (5) acquisition of prescription drugs by retail pharmacies; and (6) the retail prescription dollar. The information provided describe briefly the factors influencing price and charge setting patterns for prescription drugs. This information indicates the dynamics of the pharmaceutical market as advances in drug therapy technology and improved quality in new drug products are introduced.

In developing this report, we used Consumer Price Index (CPI) and Producer Price Index (PPI) data to analyze changes in manufacturers' prices and pharmacists' charges for prescription drugs. The CPI is a measure of the average change in retail prices paid by consumers for a fixed market basket of goods and services. The CPI for prescription drugs reflects retail prices for prescriptions sold through retail, community pharmacies. The PPI is designed to measure the change over time in the prices received in commercial transactions by manufacturers or producers from the sale of various goods. The CPI and PPI are tools that provide a consistent and reasonably reliable indicator of change over time in manufacturers' prices and pharmacists' charges for prescription drugs.

Highlights from the report's findings include:

o Between 1981 and 1986, the average annual percent change in the PPI for prescription drugs was 10.1%. The average annual percent change in the CPI for prescription drugs during the same period was 10.2%. In contrast, the average annual percent change between 1981 and 1986 in the CPI for all items was 4.2%.

In 1987 the PPI for prescription drugs increased 9.6% and in 1988 it rose 7.9%. In 1987 and 1988 the CPI for prescription drugs increased 8.0% and 7.8%, respectively.

o The rate of increase from 1981 - 1986 for the PPI indexes of specific therapeutic categories of drugs showed considerable differences. A number of explanations can be offered for these differences in inflation rates over time. The influence of single source drugs and multiple source and new chemical entities may provide a partial explanation of the differences in observed inflation rates across various therapeutic categories. However, not all PPI inflation can be attributed to developmental costs.

o The use of prescription drugs in confined to relatively few entities. The top 25 drug entities account for 28.8 percent of all drug mention; the top 500 for 88.5 percent. the drug therapy categories most commonly mentioned for the elderly during physician office visits were cardiovasculars (21.8 percent of all mentions), systemic anti-infectives (9.7 percent), diuretics (8.6 percent), analgesics (6.6 percent) and hormones (5.7 percent).

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REPORT TO CONGRESS ON

MANUFACTURERS' PRICES AND PHARMACISTS' CHARGES FOR OUTPATIENT DRUGS COVERED BY MEDICARE

INTRODUCTION

Drug coverage under Medicare Currently, with limited exceptions, Medicare covers outpatient drugs and biologicals that cannot be self-administered only when furnished incident to a physician's professional services or in certain other outpatient settings, and immunosuppressive drugs furnished within one year of a covered organ transplant. Sections 202 and 203 of the Medicare Catastrophic Coverage Act of 1988, Pub. L. No. 100-360 ("MCCA"), establishes an outpatient drug program covering catastrophic expenses for prescription drugs and insulin incurred by those persons electing Part B coverage under Medicare. Beginning on January 2, 1990, coverage includes home intravenous drugs, and extends coverage of immunosuppressive drug therapy. The program expands on January 1, 1991, to include all legend drugs, biologicals, and insulin, as now described in Section 1861(t) of the Social Security Act.

Purpose of this report Section 1834(c)(8) of the Social Security Act, as enacted by Section 202(b)(4) of MCCA, requires that the Secretary of Health and Human Services report to Congress on changes in manufacturers' prices and pharmacists' charges for covered outpatient drugs and on the use of covered outpatient drugs by individuals entitled to the benefit. The report is to include:

> "...a comparison of the increases in prices and charges for covered outpatient drugs during each 6 month period (beginning with January 1987) with the semi-annual average increase in such prices and charges during the 6 years beginning with 1981."

Although program data will provide much of the information needed to prepare subsequent reports in this series, at present there are no such data. Consequently, this initial report is based primarily upon the Producer Price Index (PPI) and the Consumer Price Index (CPI) compiled by the U.S. Department of Labor, Bureau of Labor Statistics (BLS). The PPI and CPI are readily available sources of information on changes in prices at both the manufacturer and the retailer levels. These indices were chosen as the basis for assessing change in manufacturers' prices and pharmacists' charges over time because they provide a consistent and reasonably reliable indication of price changes in similar market baskets of goods and services at regular intervals.

OVERVIEW OF THE PHARMACEUTICAL INDUSTRY

Health and drug expenditures Although spending for prescription drugs has increased over time, it has done so only at the pace of the economy in general, and more slowly than has total National health expenditures. An estimated $34 billion was spent in the United States during 1987 for prescription and nonprescription drugs and medical sundries, an increase averaging 8.9 percent per year from the $5 billion spent in 1965. In terms of the overall economy, this amount is relatively unchanged: spending for drugs and sundries ranged between 0.7 percent and 0.8 percent of the gross national product (GNP) from 1965 through 1987. However, growth in expenditure for drugs and sundries has been much slower than that for other kinds of health care, and that expenditure has fallen as a proportion of total national health expenditures, from 12.4 percent in 1965 to 6.8 percent in 1987. In particular, national expenditures for hospital care and physician services have increased much more rapidly during the past two decades than expenditures for drugs and sundries have.

Development and manufacture of prescription drugs Manufacturers of prescription drugs in the United States accounted for $37.1 billion in pharmaceutical shipments in 1988, an amount that is projected to grow by 2.8 percent in 1989 before inflation (International Trade Administration, 1989). Of the 1988 amount, $3.8 billion was exported; an additional $3.6 billion was imported. Thus, shipments destined for domestic consumption amounted to about $36.9 billion.

The process by which a prescription drug is brought to market is lengthy. The drug may be discovered, isolated, or synthesized through research and development efforts of researchers at pharmaceutical companies or in government and university settings. Once an active compound has been found, the drug must be formulated into a stable and usable dosage form. Clinical trials in animals and humans are then required by the Food and Drug Administration (FDA) as a condition for approval of a New Drug Application (NDA).

In 1987, an estimated $5.4 billion was spent by U.S. pharmaceutical companies on research and development, an annual investment that has doubled every 5 years since 1970 (Pharmaceutical Manufacturers Association, 1988). This year, pharmaceutical companies are expected to spend more on research and development than the National Institutes of Health spends on all biomedical research.

Single source and multiple source drug products For the purposes of the MCCA, it is useful to consider two types of prescription products.

Single source drugs are those for which there is no competitor. To manufacture and market a prescription drug product a company must obtain a New Drug Application (NDA). The drug discovery and development process is quite expensive, requiring investment of substantial resources in basic research, manufacturing process engineering, and clinical trials to obtain NDA approval[1]. To encourage innovation, the Federal Government grants exclusive marketing rights (i.e., patents) for a limited period of time to companies successful in discovering and obtaining NDA's for new chemical entities. During this period of exclusivity, when the drug is available only from one company, the drug is called a single source drug.

After the patent on a drug entity has expired, other manufacturers may apply for and receive FDA approval to market the drug. Once these manufacturers bring additional products to the market, the drug is generally referred to as a multiple source drug. Section 1834(c)(9) of the Social Security Act defines a multiple source drug as "an outpatient drug for which there are 2 or more drug products which are rated as therapeutically equivalent according to the Food and Drug Administration's most recent publication of 'Approved Drug Products with Therapeutic Equivalence Evaluations,'" commonly referred to as the FDA "Orange Book." The original single source product is usually referred to as the "originator" product, to distinguish it from all other products for the drug entity.

Many of the companies marketing generic or multiple source drug products are merely distributors or labelers and not the actual manufacturer of the drug product. The distributor or labeler of a drug product does not have to have an NDA to market the product as long as the actual manufacturer of the company's product holds such an NDA. There are far more distributors or labelers marketing some drugs than there are NDA holders listed in the Orange Book. For example, doxepin 25mg. capsules have 5 NDA holders listed in the Orange Book while one drug price database, Medi-Span's Generic Buying and Reimbursement Guide (GBRG), lists 23 marketed products (Attachment A). Conversely, not all NDA holders actively market a drug product under their own name. For example, 6 of the 15 NDA holders for furosemide 40mg. tablets listed in the Orange Book did not have a marketed drug product listed in GBRG (Appendix B)[2].

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[1] The Pharmaceutical Manufacturer's Association has estimated the cost of bringing a new chemical entity (NCE) to market to be $125 million dollars (Wiggins, 1987).

[2] Although the Orange Book serves as a useful reference as to which holders of NDAs produce products considered by the FDA to be therapeutically equivalent, it does not indicate which marketed drug products of drug labelers and distributors are considered by the FDA to be therapeutically equivalent.

Whether a drug is a multiple source or single source drug tends to influence the price at which the drug is marketed. Since marketers of "non-originator" or "generic" products do not incur all the research and development and marketing approval costs associated with bringing a new drug to market, their costs for entry into the market are lower than those incurred by the marketer of the originator product. Also, competition between companies marketing a drug entity tends to affect prices at which the drug can be bought and sold. As a result of these factors, many multiple source drugs undergo price decreases in the first year or two after they go off patent.

Number of prescription drugs marketed The precise number of prescription drug products on the market in the United States is not easily determined. Computerized databases (Medi-Span, Red Book, and Blue Book) use an item's national drug code (NDC) number (or other unique identifier) to index and sort drug products[3]. Although these drug databases claim to contain between 100,000 and 120,000 items, they typically include over-the-counter products, diagnostics, chemicals, pharmaceutical adjuvants, antiseptics and disinfectants, veterinary products, and soaps and sunscreens. After removal of all of the above mentioned items, the remaining database consists of legend (prescription only) pharmaceuticals for oral, topical, or injectable use in humans.

An estimate of the total number of prescription products on the market, made during January 1989 using the Master Drug Database (MDDB) maintained by Medi-Span, Inc., shows the differences that can occur when one uses various definitions of drug products. When considering the number of prescription products (as defined above) with unique NDC numbers (i.e., drug entity, dosage form, strength, manufacturer or labeler, and package size) more than 48,500 items were found. Elimination of package size in counting the number of prescription products reduced the count to a number in excess of 30,000. When only drug entity, dosage form, and strength were considered (irrespective of the number of manufacturers or labelers), there are only about 7,200 different types of prescription products on the market. Elimination of product strength from consideration when counting the number of prescription products further reduced that number to just over 4,200 drug entities in various dosage forms. Finally, there were 2,594 prescription drug entities when counted based only upon the drug (or chemical) ingredients contained in the product (Figure A).

Acquisition of prescription drugs by retail pharmacies There are several alternative channels by which prescription drug products reach the retail market.

- A majority of the large pharmaceutical companies sell their drug products to pharmacies through drug wholesalers. Drug wholesalers provide efficient distribution of, and access to, prescription drugs for many of the nation's retail pharmacies.
- A number of larger chain pharmacy operations have established their own warehousing and distribution channels. These chains usually purchase drug products in large quantities on contract. The product is then shipped from the manufacturer or distributor directly to the chain's warehouse and is, in turn, sent to the retail chain pharmacy by the chain's own distribution system.
- A few of the major pharmaceutical companies and many generic pharmaceutical companies sell drug products direct to retail pharmacies. This process is not devoid of pitfalls, however. Purchases of drug products direct from the manufacturer may require more administrative and handling costs. In addition, delivery of direct orders for drug products usually take longer than delivery from wholesalers. Also, the pharmacy is often forced to place larger orders when purchasing direct, which may result in increased inventory carrying costs.

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[3] A single NDC represents a specific drug entity, dosage form, strength, package size, and product manufacturer or labeler.

- Several retail cooperative or buying groups exist in the current retail prescription market to assist independent and small chain pharmacies in competing with the purchasing power of large chain, hospital, HMO, and mail order pharmacy operations. These retail buying groups often work with existing wholesalers to administer their group purchasing programs. However, in many cases the independent buying groups have not been given the same drug product prices as the other large purchasers mentioned above.

Although the acquisition price of a pharmaceutical products is very important when choosing among the distribution channels mentioned above, the pharmacy also considers a number of non-price factors that may significantly affect the quality of both the pharmaceutical products and pharmaceutical services provided to beneficiaries. Among these factors are:

- product availability (in stock/out-of-stock track record; ability of the supplier to meet product demand);
- product acceptability (consistent color, size, and shape; inclusion in the FDA Orange Book as an "A" rated item; and a low rate of product recalls);
- return goods policies of both the wholesaler and the product manufacturer or distributor;
- breadth of product line from the same source (both in terms of a drug entity's strengths and dosage forms and in terms of the number of drug entities in the line);
- product liability coverage by the manufacturer or distributor when the product is properly dispensed; and
- the manufacturers's cooperation with preferred channels of distribution such as prime vendor wholesalers, retail or hospital buying groups, or direct sales to a warehousing chain.

The retail prescription dollar By one count, outpatient community pharmacy prescriptions in 1986 accounted for $18.9 billion in sales, averaging $14.36 each (American Druggist, 1987). By this same count, more than 1.5 billion prescriptions were dispensed to the population as a whole, an average of 6.5 per capita.

The prescription sales dollar is typically divided among the three components of the drug distribution system: the pharmacy, the wholesaler, and the manufacturer. In 1986, for example, one report allocated 32.2 percent of the 1986 prescription dollar to the pharmacy, 5.0 percent to the wholesaler, and 62.8 percent to the manufacturer (Figure B) (Eli Lilly and Company, 1988).

The retail pharmacy share of prescription sales covers salaries, rent, and other expenses. Almost half of that share goes into salaries; another third went for other types of expenses (Table 1 and Figure C). The remainder was split fairly evenly between rent and profit. The average retail pharmacy's net before-tax profit in 1986 was 2.7 percent of gross sales.

Production and research account for nearly half of the manufacturer's share of the retail dollar. The cost of making the drug product accounts for about 36 percent of the revenue manufacturers receive or about 24 percent of the total retail prescription charge (Table 1 and Figure D). Manufacturers' research and development costs consume 11 percent of their total revenue and about 7 percent of the retail prescription charge. Marketing expenses account for about 20 percent of the manufacturers' revenue and about 13 percent of the total prescription charge. Profit (retained earnings and dividends after taxes) accounts for 15 percent of manufacturers' revenues and 9-to-10 percent of the total prescription charge.

Retailer and manufacturer profit combined consumes 12 percent of the total retail prescription charge. Based on the average prescription charge of $14.36 in 1986, retail profit amounted to about $0.39 per prescription, and manufacturers' profit was approximately $1.35 per prescription. Thus, about $1.74 of the $14.36 average prescription charge for 1986 represented profit.

PRODUCER PRICE INFLATION, 1981-1987

The producer price index The producer price index (PPI), first published in 1902, is one of the oldest statistical series published by the U.S. Department of Labor (Bureau of Labor Statistics, 1984). The PPI is designed to measure the change over time in the prices received in commercial transactions by manufacturers or producers of various goods.

The Bureau of Labor Statistics attempts to base the PPI on actual transaction prices. Companies are requested to report prices less all discounts, allowances, rebates, free deals, etc., so that the resulting net price is the actual selling price of the product being surveyed. The validity of the PPI, then, is dependent largely upon the accuracy with which manufacturers in a given industry report true transaction prices for their products.

One limitation of the PPI particularly relevant to the pharmaceutical industry is the difficulty in accounting for the rapid introduction of new products and any improved quality they may deliver (Bureau of Labor Statistics, 1989). New chemical entities or improved dosage forms introduced into the retail prescription market may provide a significant therapeutic advance over existing products. Usually, new patent-protected products cost more than existing products on the market, partly reflecting that advance. However, the addition of these new products to the PPI will result in a measured price increase, rather than a reflection of the improved quality or technological advance represented by the new products, resulting in an upward bias of unknown magnitude to price inflation as measured by the PPI.

Any price index incorporates some level of aggregation, and the PPI is no exception. The PPI series includes separate price measures for some three dozen therapeutic categories of drug products, as well as a composite index for all prescription drugs.

Producer price inflation General trends in manufacturers' prices for drug products can be observed by reviewing changes over time in the PPI for prescription drugs. A summary of these changes for several therapeutic categories of prescription drugs are summarized in Table 2. The PPI for all prescription products grew 78.3 percent between 1981 and 1986, averaging 10.1 percent per year. In recent years, growth has fallen below the longer-term average (Figure E): the 1986-87 change was 9.6 percent and that between 1987 and 1988 was 7.9 percent.

Considerable differences exist among price inflation for specific therapeutic categories. Prices of broad spectrum penicillins and anticoagulants increased only 14.5% and 16.6%, respectively, between 1981 and 1986 (Figure F). This rate of change was lower than the 28-percent general rate of inflation (measured by the consumer price index for all consumer items), and considerably below the 78-percent growth in the aggregate PPI for prescription drugs. The price of antiarthritics also increased at a rate (30.8 percent) similar to the overall rate of inflation.

In contrast, prices in five of the therapeutic categories increased between 1981 and 1986 more than four times the general price increase in the economy (Figure G). Cancer therapy drug prices grew 159.3 percent at the producer level, dermatologicals experienced inflation of 155.4 percent, sedative prices rose 132.8 percent, central nervous system (CNS) stimulant prices rose 129.6 percent, and psychotherapeutic prices grew 113.2 percent. In addition, price levels for analgesics grew at a 6-year rate of 105.3 percent, almost four times the general level of price inflation.

Reasons for producer price growth The influence of single source and multiple source drugs and new chemical entities may provide a partial explanation of the difference in observed inflation rates across the various therapeutic categories. Those categories experiencing relatively low inflation (broad spectrum penicillins, for example, or anticoagulants) contain a large number of off-patent or multiple source drugs. Similarly, ibuprofen, a major antiarthritic drug, went off-patent during the period under consideration, potentially lowering the growth of prices in that category. Other therapeutic categories may have experienced more rapid price growth because of the introduction of new chemical entities carrying higher price tags due to embodied improvements in quality or effectiveness.

Not all producer price inflation can be attributed to development costs, however. Testimony before the House Subcommittee on Health and the Environment resulted in a staff report in which the following major findings appeared:

o Twenty-two of the 24 companies responding to the House survey had increases in revenues from price changes that were greater than increases in expenditures for research and development (R&D) for the period 1982-1986.

o Marketing and detail staff expenditures were greater than R&D expenditures during the same period.

o Prices charged in the United States are consistently higher than those charged in foreign countries for the same drug.

CONSUMER PRICES FOR PRESCRIPTION DRUGS

The consumer price index The consumer price index (CPI), a measure of the average change in retail prices paid by consumers for a fixed market basket of goods and services, is widely used as a measure of inflation in the consumer economy. The all urban index (CPI-U) is a market basket weighted to represent the buying habits of about 80 percent of the non-institutional population of the United States (Bureau of Labor Statistics, 1984). Unless otherwise noted, all CPI values used in this report are data from the CPI-U, unadjusted for seasonal variation.

The CPI for all items is based on a sample of prices for food, clothing, shelter and fuels, transportation, medical services, and the other goods and services that people buy for daily living. Price change is measured by gathering prices on essentially the same market basket of goods and services at regular intervals and comparing such prices with an earlier base period. In this way, the CPI is not an exact measure of price change; as with the PPI, non-price escalation of the CPI may occur due to changes in technology or significant increases in product or service quality.

Even though the CPI is an indicator of retail prices, it does not reflect retailer actions alone. In the pharmaceutical market, for example, the pharmacy's acquisition cost from manufacturers and wholesalers typically represents 67% to 75% of the total retail prescription price. Therefore, to isolate the change in retail prices contributed by the retailer requires first that one subtract any increase in the cost of goods sold.

As with the PPI, there are subcategories for the CPI as well as aggregate indexes. At the most aggregate level, the CPI for all items (housing, food, clothing, medical care, etc.) is a measure of economy-wide price change. A CPI series for all medical care items is routinely reported by BLS and is further divided into two major subdivisions: "medical care services" and "medical care commodities." Medical care commodities aggregate two groupings: "prescription drugs" and "non-prescription drugs and medical supplies." Until the end of 1986, the BLS also maintained a CPI series for each of six specific therapeutic category groupings of prescription products.

It should be noted that the CPI for prescription drugs (CPI-Rx) reflects retail prices for prescriptions sold through community pharmacies. Although the PPI for prescription drugs reflects manufacturers' prices to such retailers, the PPI also encompasses manufacturers' prices to other classes of trade such as hospitals, health maintenance organizations, and mail service pharmacies, none of which are included in the CPI.

Consumer price inflation for prescription drugs Changes in retail prices for prescription drugs over time are reflected in the CPI-Rx. This component increased 79.4 percent increase between 1981 and 1986 (Table 3), an average annual rate of 10.2 percent. As was the case for the PPI, the CPI-Rx grew more slowly than that average during 1987 and 1988 (Figure H): the inflation rates posted were 8.0 percent and 7.8 percent, respectively.

Prescription drug prices at the retail level have grown more rapidly than the general rate of inflation, but at about the same rate as drug prices at the producer level (Figures I and J). In contrast to the 10.2 percent average growth of drug prices between 1981 and 1986, the CPI for all items experienced a rate of 4.2 percent; annual growth in 1987 and in 1988 was 4.4 percent. Indeed, the CPI-Rx has risen more rapidly since 1980 than any other component of the CPI for medical care (Figure K). On the other hand, the nearly parallel increase in the prescription drug components of the PPI and the CPI is an indication that manufacturers' drug product prices are a major factor affecting growth retail prescription prices.

The current situation, in which prescription drug price inflation outpaces that of consumer goods and services in general, has not always been the case; between 1970 and 1980, the opposite was true. In fact, the CPI-Rx actually fell in 1972 and again in 1973 (Figure L).

Other measures of retail costs The CPI-Rx is not the only measure of retail prices. For example, Eli Lilly and Company have surveyed retail pharmacies for many years; between 1981 and 1986, their average prescription price grew from $8.80 to $14.36, an aggregate increase of 63.2 percent (Eli Lilly and Company, 1988), compared to the 79.4 percent increase posted for the CPI-Rx. The Lilly price increased 7.0 percent between 1986 and 1987, compared to 8.0 percent for the CPI-Rx. Some of the difference between the two rates of inflation can be attributed to the composition of the index: the CPI-Rx holds fixed the mix of drugs to be priced, while the Lilly index reflects the average of all drugs sold, incorporating changes in price and mix.

It is also instructive to compare the growth in the retail portion of prescription prices with the manufacturers' share of that price. The gross margin per prescription in independent pharmacies grew from $3.02 in 1981 to $4.62 in 1986, an increase of 53.0 percent over the 6-year period. Thus, the rate of increase in pharmacists' charges was about one-third less than the rate of increase in manufacturers' prices. The 1987 average gross margin was $4.93, 6.7 percent higher than in 1986, compared to an increase of 7.9 percent in the PPI. Over the last thirty years, there has been a slight but steady decline in net pre-tax profit as a percent of sales, beginning at about 5.5 percent in 1960 and reaching 3.3 percent in 1987.

USE OF OUTPATIENT DRUGS BY THE AGED POPULATION

Hard data on use of drugs by the Medicare population are not currently available. Fragmentary evidence on use by subgroups of the population was being compiled at the time this report was prepared, and will be submitted to Congress under separate cover.

Data on "drug mentions" may shed some light on use patterns by the aged population, however. The National Disease and Therapeutic Index (NDTI) provides an estimate of the types and number of drugs mentioned during office-based physician visits (IMS America, 1989); a "drug mention" can be a prescription, provision of a free sample, a hospital order, and so on, making it difficult to isolate prescription activity alone. However, the patterns of drug mentions can provide clues to use of drugs by the aged population.

The first piece of useful information provided by the drug mention data is that use of prescription drugs is confined principally to relatively few entities (Table 4 and Figure M). Drug mentions for the elderly in 1988 included almost 2,500 different drug entities and about 30,000 unique drug products (i.e., drug entity, dosage form, strength, and labeler or manufacturer). However, the top 25 drug entities accounted for 28.8 percent of all drug mentions and the top 100 drug entities included 56.2 percent of all drug mentions. The top 250 drug entities were responsible for 75.9 percent of all drug mentions and the top 500 were responsible for 88.5 percent of all drug mentions.

The drug therapy categories most commonly mentioned for the elderly during physician office visits were cardiovasculars (21.8 percent of all mentions), systemic anti-infectives (9.7 percent), diuretics (8.6 percent), analgesics (6.6 percent), and hormones (5.7 percent) (Table 5).

SUMMARY

Between 1981 and 1986, both producer and retail prescription drug prices increased more than twice as fast as consumer prices in general. However, since 1987, the gap between drug inflation and general inflation has narrowed.

More than two thirds of the retail price of prescription drugs goes to pay for the prices of the drug products obtained from manufacturers or wholesalers. This may explain the close relationship seen in the level of increase in prescription drug prices at the manufacturer level and pharmacists' charges for prescription drug at the retail level.

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TABLE 1

THE 1986 AVERAGE PRESCRIPTION

Cost Contribution by Source

SOURCE	SOURCE COST (PERCENT)		PERCENT OF TOTAL COST	AGGREGATE PERCENT
PHARMACY	$ 4.62			32.2%
Salary	$ 2.28	(49.4%)	15.9%	
Expenses	$ 1.62	(35.1%)	11.3%	
Rent	$ 0.33	(7.1%)	2.3%	
Net Profit (before taxes)	$ 0.39	(8.4%)	2.7%	
WHOLESALER	$ 0.72			5.0%
MANUFACTURER	$ 9.02			62.8%
Cost of Goods Sold	$ 3.25	(36.0%)	24.4%	
Marketing	$ 1.86	(20.6%)	13.0%	
Research and Development	$ 1.04	(11.5%)	7.2%	
Distribution and Administration	$ 0.78	(8.6%)	5.4%	
Corporate Taxes	$ 0.76	(8.4%)	5.3%	
Net Earnings*	$ 0.72	(8.0%)	5.0%	
Dividends*	$ 0.63	(7.0%)	4.4%	
TOTAL	$14.36		100%	100%

* Net earnings and dividends combined represent corporate profits after taxes at the manufacturer level and account for $ 1.35 of the average prescription price, 9.4% of the average prescription price, and 15.0% of the manufacturers portion of the average prescription price.

(Source: Compiled by the Pharmaceutical Economics Research Center from data found in the Lilly Digest, 1987 and data from Eli Lilly and Company.)

TABLE 2

PPI SERIES	1981 - 1986 PERCENTAGE CHANGE	81-86 AVERAGE SEMI-ANNUAL PERCENTAGE CHANGE	81-86 AVERAGE ANNUAL PERCENTAGE CHANGE	SEMI-ANNUAL PERCENTAGE CHANGE 6/87	12/87	6/88	12/88	ANNUAL PERCENTAGE CHANGE 87	88
PPI SERIES (1982=100)									
Pharm. Preps.	56.2	4.2	8.5	4.0	2.8	3.8	3.7	6.9	7.5
Rx Products	70.3	4.9	10.1	5.7	3.7	3.8	4.1	9.6	7.9
Analgesics	105.3	6.3	12.8	2.2	10.8	5.9	4.7	13.3	10.2
Narc. Analgesics	86.5	5.8	11.4	5.8	12.3	3.4	19.9	16.1	19.9
Antiarthritics	30.8	2.8	4.3	5.4	2.7	1.1	3.6	8.3	7.5
Anticoagulants	16.6	--	--	-0.3	8.6	--	--	8.3	--
Anticonvulsants	80.9	--	--	3.8	12.9	9.3	0.0	17.2	9.3
Systemic Anti-inf.	52.7	3.6	6.2	5.2	2.9	3.1	4.4	8.3	7.8
Broad Spectrum Antibiotics	41.2	3.2	5.9	3.9	3.1	2.1	3.4	7.1	5.9
Broad Spectrum Penicilline	14.5	-0.2	2.8	2.3	0.0	--	--	2.3	--
Cancer Therapy	159.3	14.3	21.4	5.4	9.5	3.2	4.8	15.3	8.2
Cardiovasculars	98.9	6.0	12.1	4.1	2.7	5.2	2.8	6.9	9.1
Antihypertensives	76.7	5.4	11.6	7.4	4.1	5.5	0.1	11.8	5.2
Vasodilators	65.4	5.1	10.5	0.9	0.0	7.9	4.3	0.4	8.4
CNS Stimulants	129.6	7.5	15.7	7.7	2.6	10.6	2.2	10.5	13.0
Cough & Cold Rem.	75.7	4.8	9.8	4.2	3.4	5.5	3.3	7.7	8.9

PPI SERIES	1981 - 1986 PERCENTAGE CHANGE	81-86 AVERAGE SEMI-ANNUAL PERCENTAGE CHANGE	81-86 AVERAGE ANNUAL PERCENTAGE CHANGE	SEMI-ANNUAL PERCENTAGE CHANGE 6/87	12/87	6/88	12/88	ANNUAL PERCENTAGE CHANGE 87	88
Dermatologicals	155.4	8.3	17.2	1.8	0.9	2.6	5.1	2.7	6.1
Diurectics	54.8	4.1	7.7	7.1	3.4	-0.6	4.3	10.7	6.9
Hormones	36.9	4.0	5.4	8.3	-8.0	2.8	3.3	-0.3	7.7
Psychotherap.	113.2	7.1	14.9	10.5	8.1	4.1	4.9	19.4	11.9
Sedatives	132.8	10.8	18.7	--	--	9.2	3.7	--	13.2
Vitamins	36.7	3.3	6.4	3.7	0.0	3.9	9.4	3.7	13.6

TABLE 3

CPI SERIES	1981 - 1986 PERCENTAGE CHANGE	81-86 AVERAGE SEMI-ANNUAL PERCENTAGE CHANGE	81-86 AVERAGE ANNUAL PERCENTAGE CHANGE	SEMI-ANNUAL PERCENTAGE CHANGE 6/87	12/87	6/88	12/88	ANNUAL PERCENTAGE CHANGE 87	88
CPI NEW SERIES (1982-84=100)									
All CPI Items	28.0	2.1	4.2	2.7	1.7	2.3	2.1	4.4	4.4
All Medical Care Items	62.1	4.1	8.4	3.3	2.5	3.8	3.0	5.8	6.4
Medical Commodities	60.3	4.0	8.2	3.8	3.1	3.3	3.4	7.1	6.9
Rx Drugs	79.4	5.0	10.2	4.0	3.8	4.0	3.7	8.0	7.8
OTC Drugs	52.0	3.6	7.3	3.8	2.2	2.0	3.3	6.1	5.3
Physicians' Services	57.7	3.9	7.9	3.9	2.3	4.8	2.6	6.3	7.5
Dental Services	51.0	3.5	7.1	4.5	2.6	4.0	2.5	7.2	6.7
Hospital Room	75.6	4.8	9.9	2.5	4.0	5.2	5.0	6.6	10.4
Outpatient Services	--	--	--	2.3	4.7	3.7	5.3	7.1	9.2
All Items Less Medical Care	26.4	2.0	3.9	2.6	1.6	2.2	2.0	4.2	4.1

TABLE 4

DRUG ENTITIES AND DRUG MENTIONS USED BY THE ELDERLY

Cumulative # of Drug Entities	Cumulative % of Drug Entities	Cumulative % of Drug Mentions (1,000)
25	1.0	28.8
50	2.1	41.6
75	3.1	50.0
100	4.1	56.2
125	5.2	60.8
150	6.2	64.7
175	7.2	68.1
200	8.3	71.0
225	9.3	73.6
250	10.3	75.9
275	11.3	77.9
300	12.4	79.6
325	13.4	81.2
350	14.4	82.6
375	15.5	83.8
400	16.5	84.9
425	17.5	86.0
450	18.6	86.9
475	19.6	87.7
500	20.6	88.5
600	24.8	91.1
800	33.0	94.4
1000	41.3	96.4
1200	49.5	97.7
1600	66.0	99.0
2000	82.5	99.7
2424	100.0	100.0

SOURCE: IMS America

TABLE 5

DRUG MENTIONS BY THERAPEUTIC CATEGORY FOR THE ELDERLY

Therapeutic Category	% by Category	Cumulative % by Category
Cardiovascular	21.8	21.8
Anti-Infective, Systemic	9.7	31.5
Diuretics	8.6	40.1
Analgesics	6.6	46.7
Hormones	5.7	52.4
Respiratory Therapy	5.5	57.9
Diabetes Therapy	5.1	63.0
Antiarthritics	5.0	68.0
Ophthalmic Preparations	4.7	72.7
Psychotherapeutics	4.3	77.0
Antispasmodics (GI/GU)	3.5	80.5
Nutrients & Supplements	2.1	82.6
Dermatologicals	1.2	83.8
Anticoagulants	1.2	85.0
Cough/Cold Preps (Rx)	1.1	86.1
Thyroid Therapy	1.0	87.1
Hematinics	1.0	88.1
Sedatives	1.0	88.1
Laxatives	0.8	89.7
Vitamins (Rx)	0.8	90.7
Cancer Therapy	0.8	91.5
Cholesterol Agents/Lipotropils	0.7	92.2
Antinauseants	0.6	92.8
Anti-Parkinsonism Agents	0.6	93.4
Antihistamines, Systemic	0.6	94.0
Antacids (Rx)	0.6	94.6
Other Categories	5.4	100.0

SOURCE: IMS America

FIGURE A

NUMBER OF MARKETED DRUG PRODUCTS

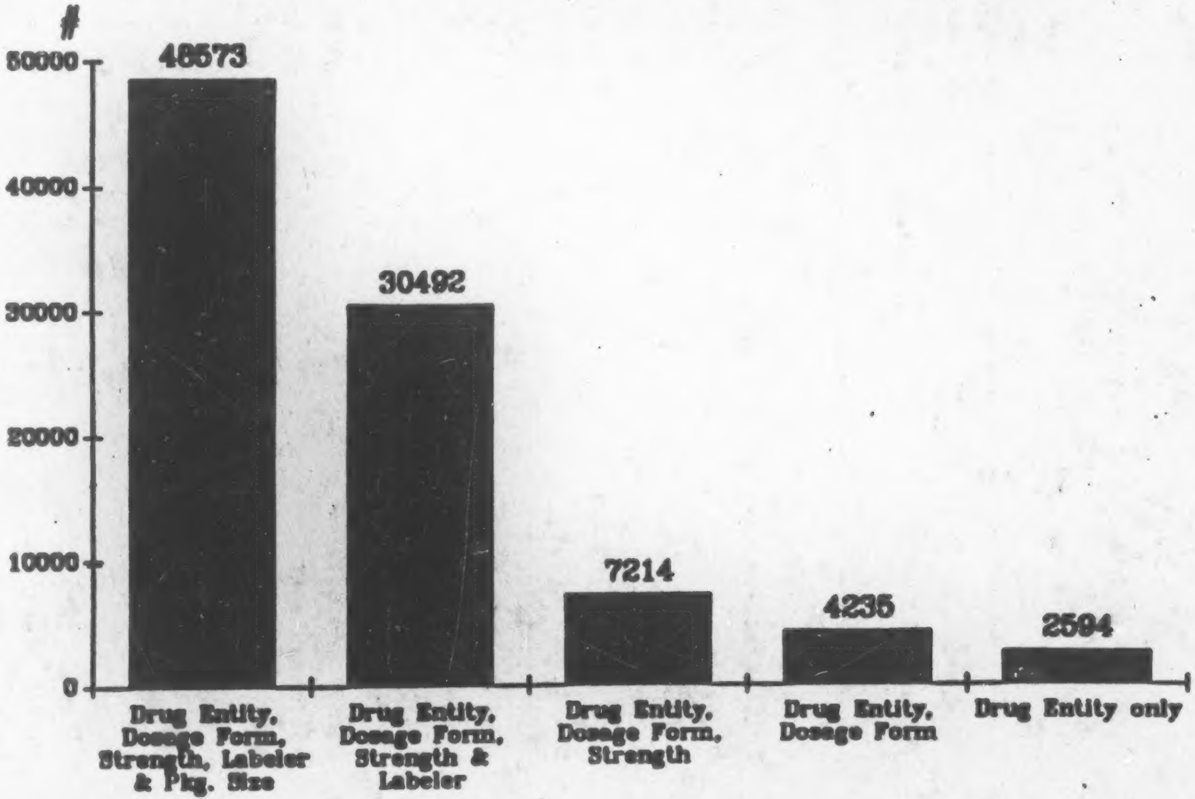
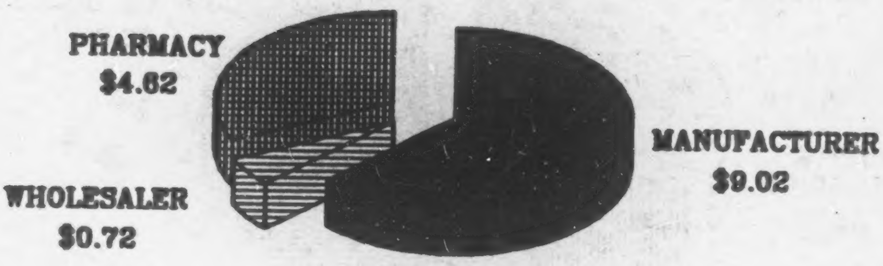


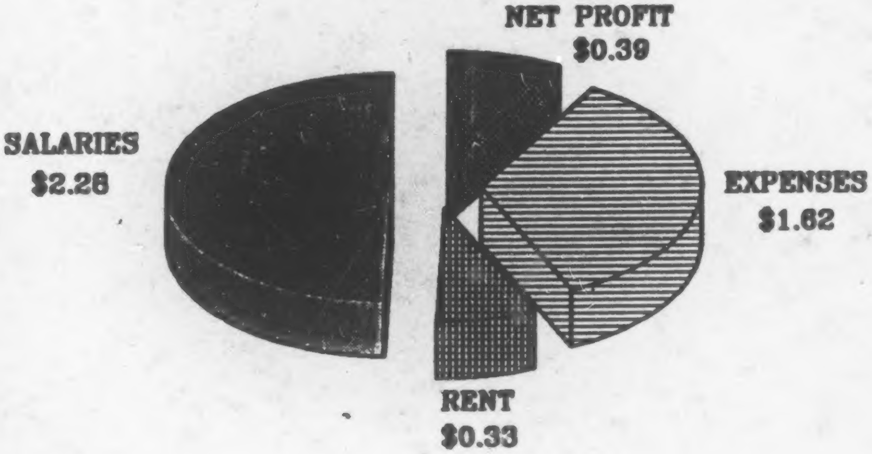
FIGURE B



1986 AVERAGE PRESCRIPTION

1986 AVG. Rx PRICE = $14.36

FIGURE C



1986 AVERAGE PRESCRIPTION

1986 AVG. Rx PRICE = $14.36

PHARMACY COMPONENT = $ 4.62

FIGURE D

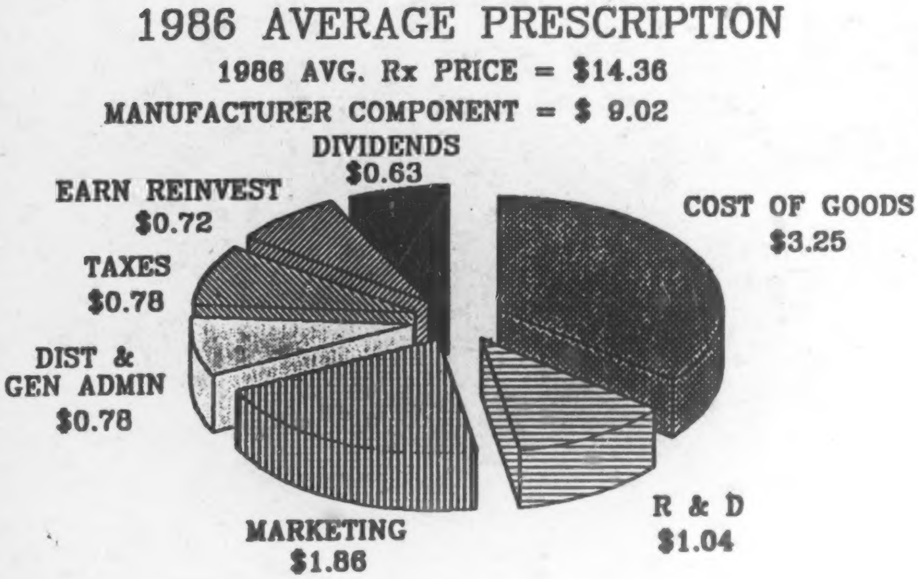
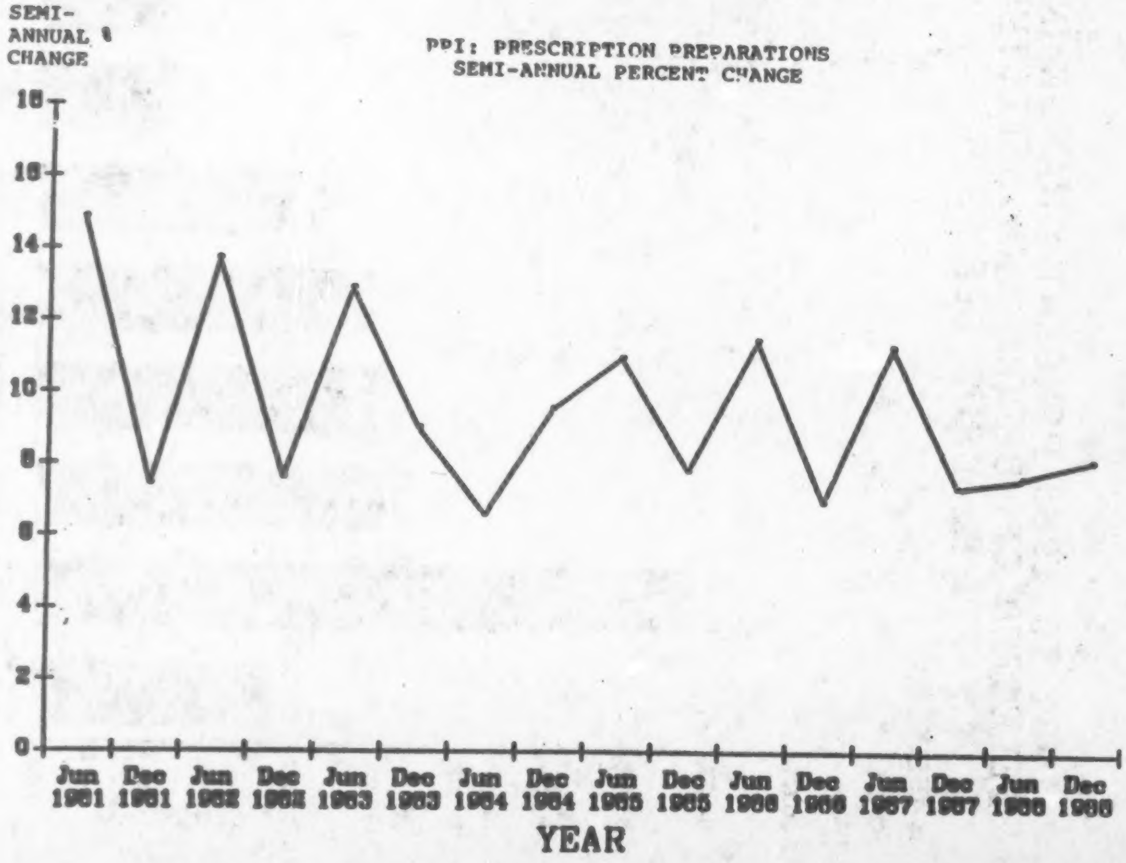

1986 AVERAGE PRESCRIPTION
1986 AVG. Rx PRICE = $14.36
MANUFACTURER COMPONENT = $ 9.02
DIVIDENDS
$0.63
EARN REINVEST
$0.72
TAXES
$0.78
DIST &
GEN ADMIN
$0.78
MARKETING
$1.86
R & D
$1.04
COST OF GOODS
$3.25

FIGURE E



PPI: PRESCRIPTION PREPARATIONS
SEMI-ANNUAL PERCENT CHANGE

FIGURE F

1981 TO 1986 PERCENT CHANGE IN SELECTED CPI SERIES AND SELECTED PPI Rx DRUG SERIES: I

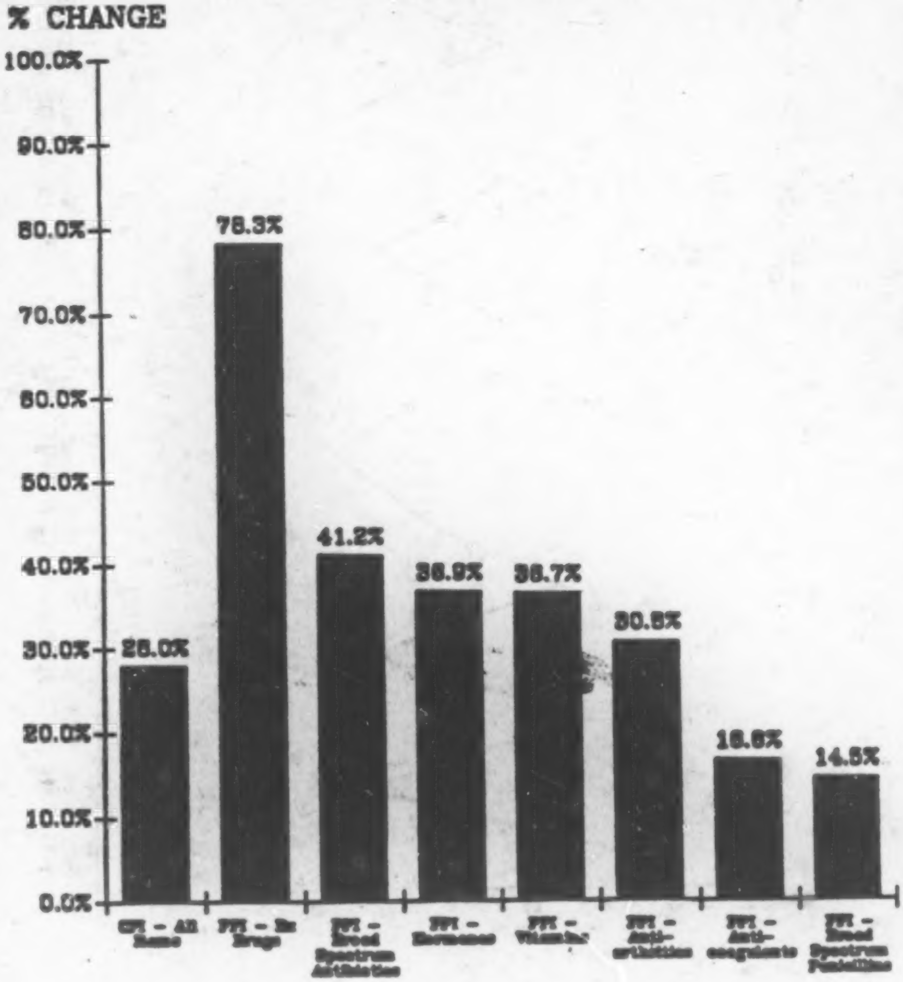


FIGURE G

1981 TO 1986 PERCENT CHANGE IN SELECTED CPI SERIES AND SELECTED PPI Rx DRUG SERIES: II

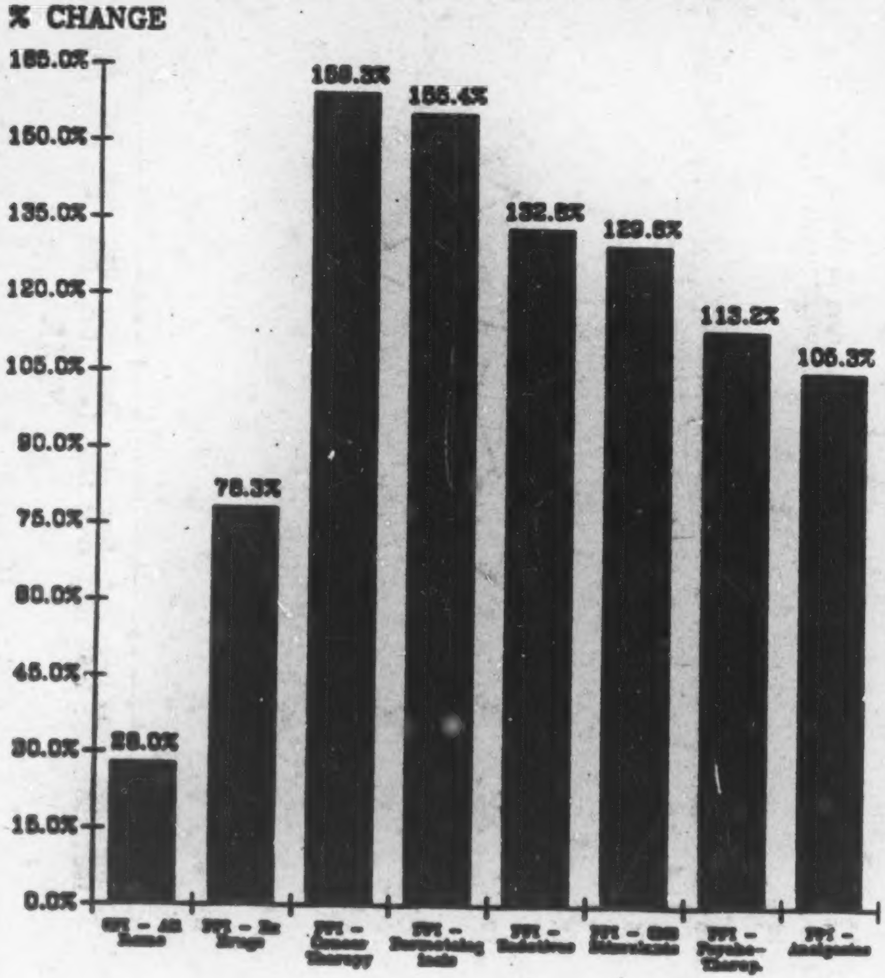


FIGURE H

CPI: PRESCRIPTION DRUGS
SEMI-ANNUAL PERCENT CHANGE

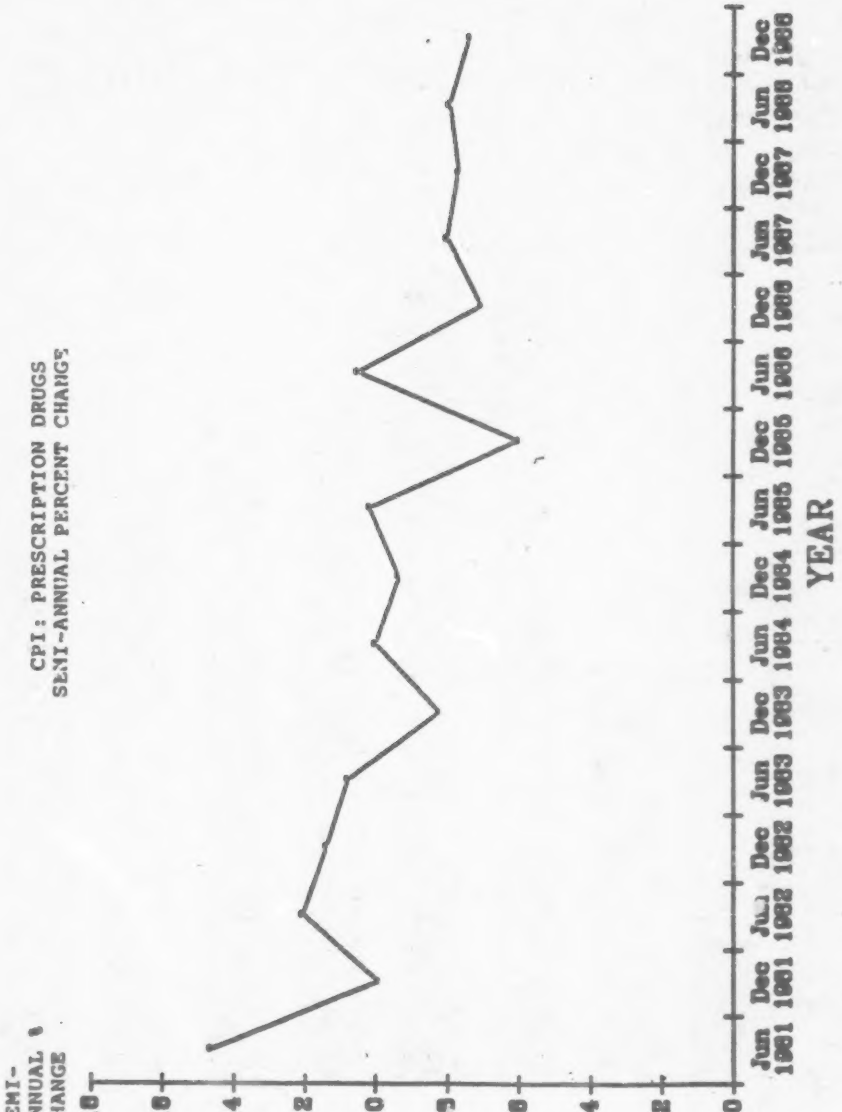


FIGURE I

PRODUCER AND CONSUMER PRICE INDEXES
SEMI-ANNUAL PERCENT CHANGE

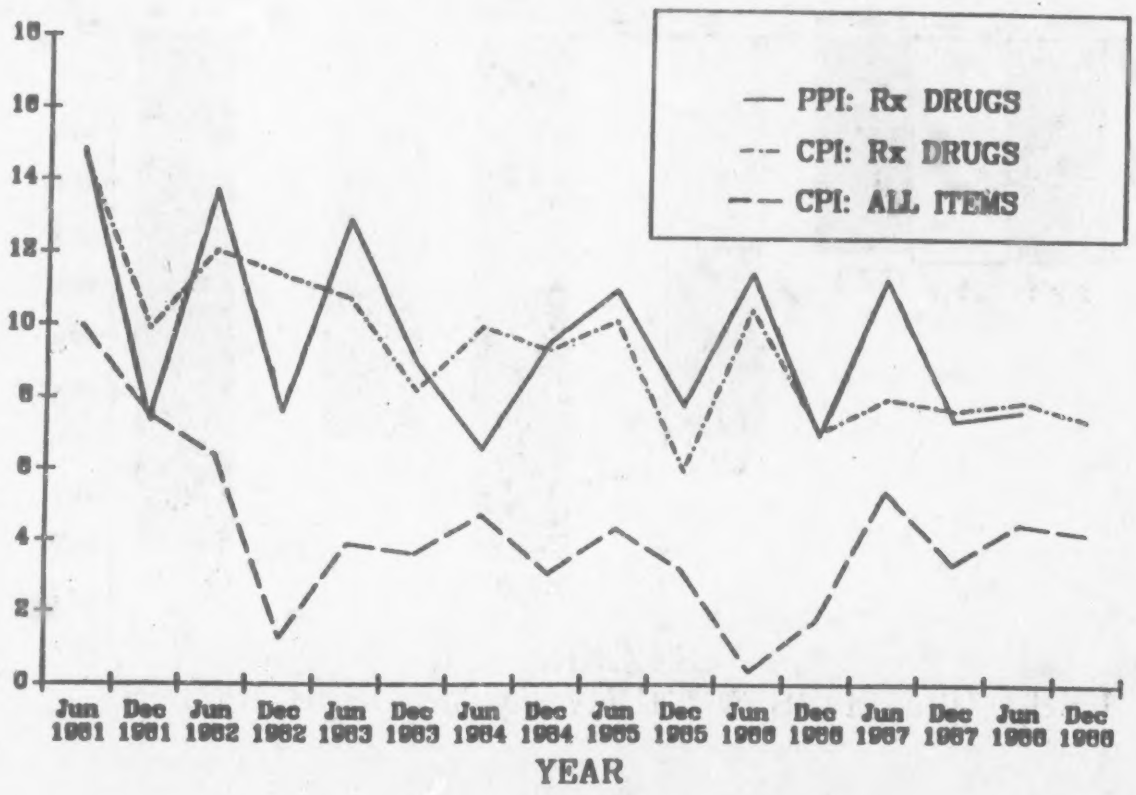
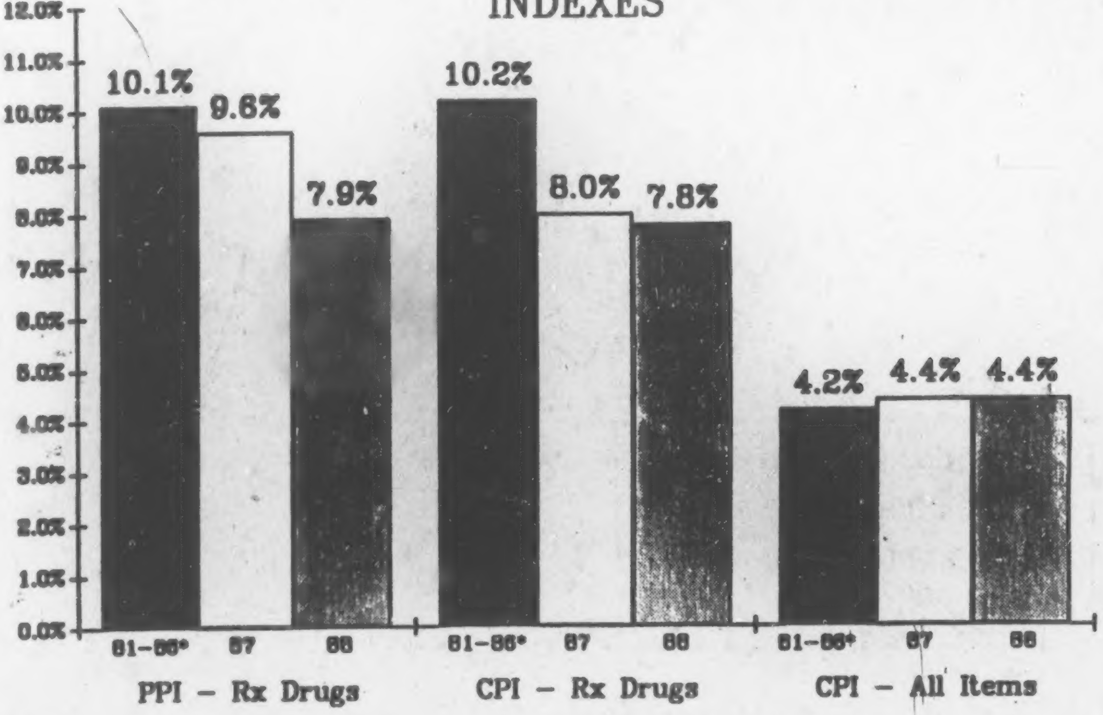


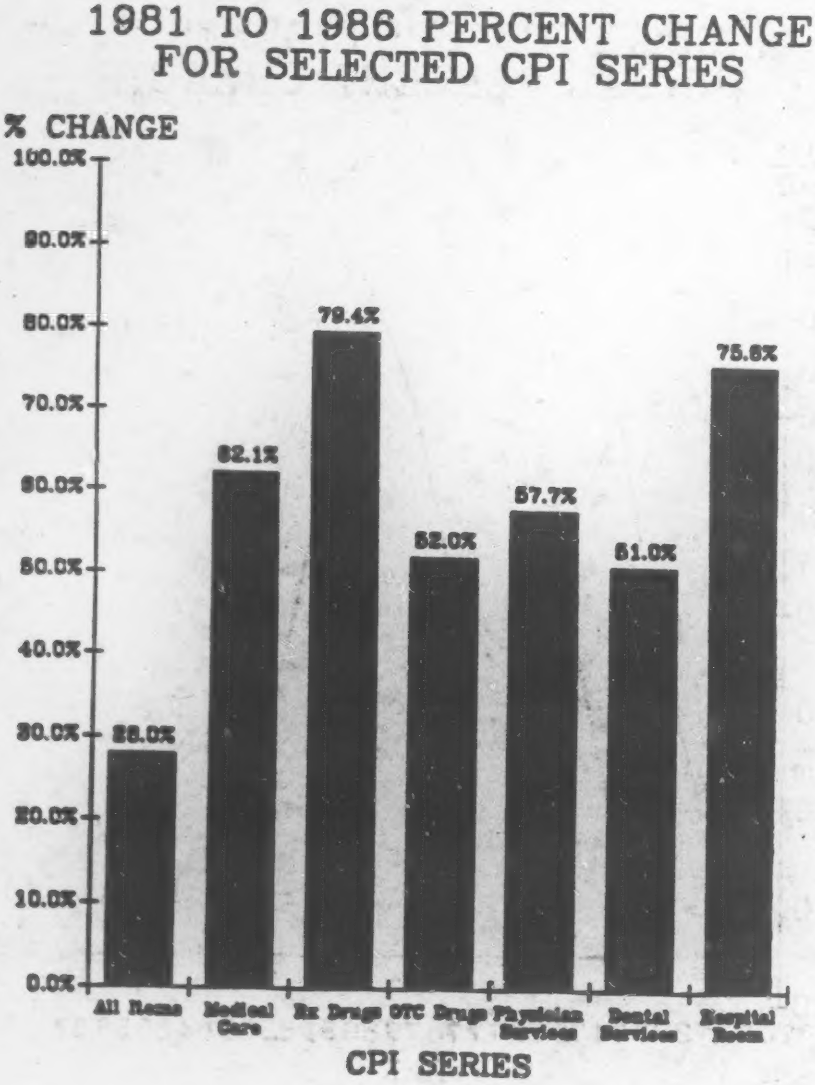
FIGURE J

ANNUAL PERCENT CHANGE IN SELECTED PRICE INDEXES



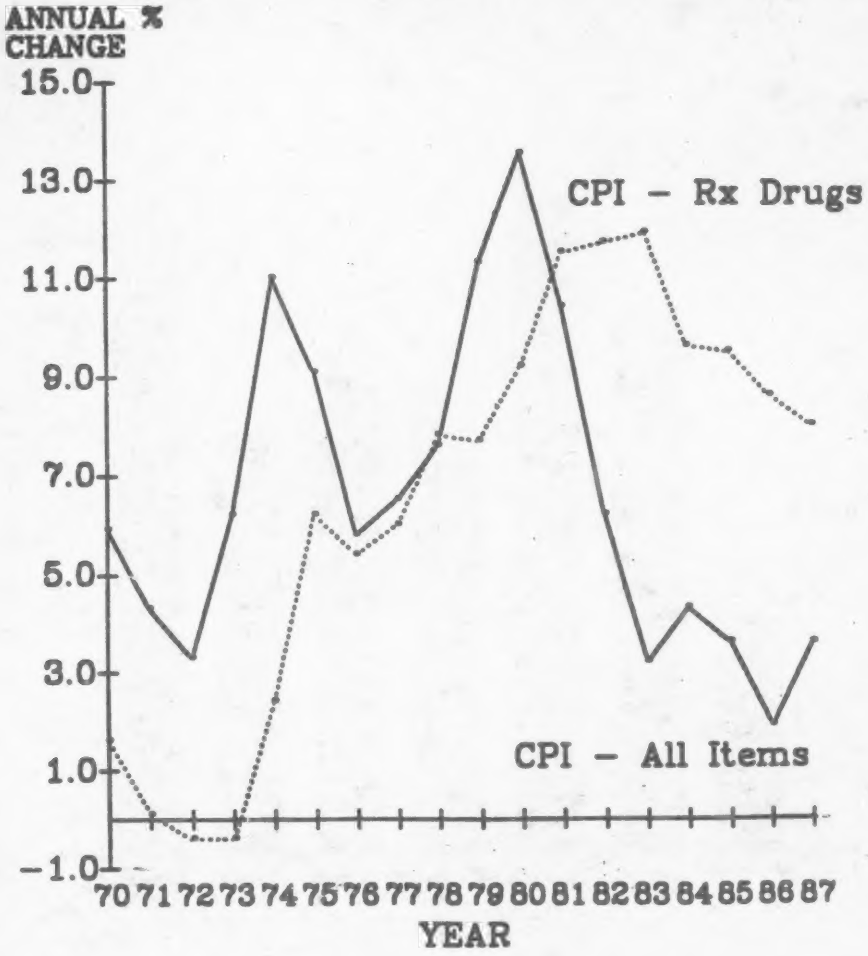
* Average Annual Percent Change

FIGURE K



1981 TO 1986 PERCENT CHANGE FOR SELECTED CPI SERIES

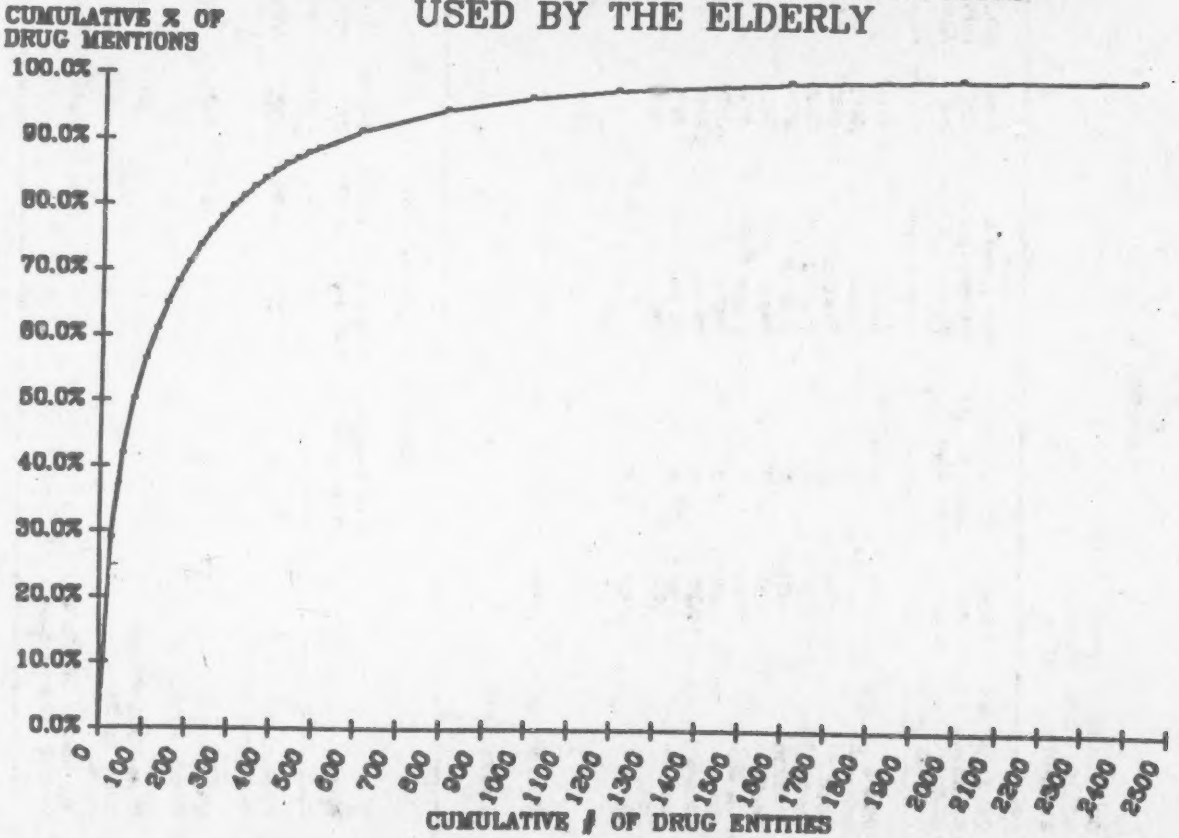
FIGURE L



SELECTED CPI INDEXES: ANNUAL PERCENT CHANGE

FIGURE 14

DRUGS ENTITIES AND DRUG MENTIONS USED BY THE ELDERLY



APPENDICES

APPENDIX A

DRUG NAME: Doxepin
DOSAGE FORM: Capsules
STRENGTH: 25 mg

Mfr. Listed in Medispan's GBRG	Price Per Unit	Mfr. w/NDA Listed in FDA Book	Mfr. Listed in Medispan's GBRG	Price Per Unit	Mfr. w/ NDA Listed in FDA Book
Bioline	.1110	N	Mylan	.1312	Y
Danbury	.1180	N	Parmed	.1223	N
Dixon	.1113	N	Pennwalt*	.1769	Y
Geneva Gen.	.0750	N	Purepac	.0806	N
Glenlawn	.0821	N	Qualitest	.0874	N
Goldline	.1275	N	Regal	.0885	N
H.L. Moore	.0884	N	Roerig (Pfizer*)	.2323	Y
Harber	.1440	N	Rugby	.1169	N
Lederle	.1287	N	Schein	.0861	N
Lemmon	.0784	N	Tx Drug Rep	.0900	N
Major	.1117	N	URL	.1230	N
Mutual	.1227	N			

NDA's for which no product is marketed direct by NDA holder:

Chelsea; Cord

SUMMARY OF COMPARISON

Source	# of Products /NDAs Listed	# of Manu-facturers	Lowest AWP	Highest AWP	Average AWP**
Products in Medispan's GBRG	23	23	.0750	.2323	.1079
NDAs in FDA's Orange Book	5	5	.1312	.2323	.1801
NDAs Not Marketed Direct By Mfr.	2	2	—	—	—
Net Marketed Products in FDA's Orange Book	3	3	.1312	.2323	.1801

* Items underlined are either the product patent holder, originator, or a licensee while the product was under patent. Data from Medispan's Generic Pricing and Reimbursement Guide are from the October 1987 edition.

** Average AWP is the average of all AWPs for each generic drug in a given category not including the reference, or branded drug.

APPENDIX B

DRUG NAME: Furosemide
DOSAGE FORM: Tablets
STRENGTH: 40 mg

Mfr. Listed in Medispan's GBRG	Price Per Unit	Mfr. w/NDA Listed in FDA Book	Mfr. Listed in Medispan's GBRG	Price Per Unit	Mfr. w/ NDA Listed in FDA Book
Ascher	.0633	N	Mallard	.0210	N
Ascot	.1084	N	Mutual	.0227	N
Barr Labs	.0243	Y	Mylan	.0350	Y
Best Generic	.0285	N	Parmed	.0337	N
Bioline	.0210	N	Perrigo	.0296	N
Cenci	.0713	N	Purepac	.0473	N
Cooper Drug	.0294	N	Qualitest	.0146	N
Copley	.0395	N	Regal	.0420	N
Danbury	.0257	Y	Roxane	.0391	Y
Dixon	.0250	N	Ruckstahl	.0585	N
Genetco	.0300	N	Rugby	.0473	N
Geneva Gen.	.0205	N	Schein	.0250	N
Glenlawn	.0246	N	Searle Lab	.0634	N
Goldline	.0415	N	Super Pharm.	.0355	Y
H & H Labs	.1495	N	Towne-Paulson	.0396	N
H.L. Moore	.0469	N	Tx Drug Rep	.0240	N
Herber	.1110	N	UDL Labs	.0480	N
Heather	.0450	N	URL	.0340	N
Hoechst	.1145	Y	Vangard	.0183	N
Interstate	.0300	N	Vitarine	.0325	Y
Lannett	.0560	N	Warner Chil	.1018	N
Lederle	.0838	Y	Westward	.1084	N
Lemmon	.1208	N	Williams	.0219	N
Major	.0480	N	Zenith	.0209	Y

NDA's for which no product is marketed direct by NDA holder:
Chelsea; Cord; Intl Med Sys; Kalapharm; Parke Davis; Watson

SUMMARY OF COMPARISON

Source	# of Products /NDAs Listed	# of Manufacturers	Lowest AWP	Highest AWP	Average AWP
Products in Medispan's GBRG	48	48	.0146	.1208	.0468
NDAs in FDA's Orange Book	15	15	.0243	.1145	.0457
NDAs Not Marketed Direct By Mfr.	6	6	—	—	—
Not Marketed Products in FDA's Orange Book	9	9	.0243	.1145	.0457

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* Items underlined are either the product patent holder, originator, or a licensee while the product was under patent. Data from Medispan's Generic Ranking and Reimbursement Guide are from the October 1987 edition.

APPENDIX 4

ADDITIONAL INFORMATION ON PHYSICIANS' KNOWLEDGE OF DRUG PRICES

PRE-PUBLICATION COPY

CONFIDENTIAL

An Exploratory Study of Physician Perceptions of Drug Price Information and a Prescription Price Newsletter

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INTRODUCTION

Examination of various strategies designed to contain health care costs, including those for ethical pharmaceutical products, is an area of much interest to providers, fiscal intermediaries and other third party payors, and consumers alike. Interest in the evaluation of those strategies will undoubtedly grow in the future with rapidly escalating costs for medical services. Expenditures for personal health care topped 435 billion dollars in 1987 and are projected to increase to almost 1.4 trillion dollars in the year 2000[1].

As ethical pharmaceuticals play an ever increasing role in patient care, personal expenditures for pharmaceuticals and devices are projected to increase from 33 billion dollars in 1987 to 103 billion dollars in 2000[1]. Estimating pharmaceutical expenditures accurately may be difficult due to the influence of, for example, new product introductions, biotechnology research and development, and innovations in pharmaceutical marketing such as direct-to-consumer prescription drug advertising. These and other factors will likely have unpredictable effects on drug use[2]. It is predictable, however, that new drug therapies will command premium prices and that the cost of drug therapies will continue to increase.

One of the available strategies to contain future expenditures for pharmaceuticals is to persuade physicians to prescribe the most cost effective product(s) for a given condition by providing physicians with accurate drug cost information. An 'information' strategy such as this has appeal but may not be successful since it is generally accepted that physicians are poorly informed about the cost of the pharmaceuticals they prescribe. In general physicians have demonstrated poor overall accuracy for predicting prices for prescriptions[3]. They tend to greatly overestimate the prices of the less expensive legend drugs and greatly underestimate the more expensive products. This study also provided evidence that physicians who claim they are confident about prescription costs are generally no better estimators of prices than those physicians who are less confident. Further, medical residents who indicated that they relied on price information from pharmacists were more accurate estimators of prescription prices than were practicing physicians who relied on information from manufacturers' representatives[3]. This implies that the source of price information may also be a factor relating to the accuracy of price predictions by physicians.

If an information strategy for reducing prescription expenditures is to be effective, physicians should perceive significant need for price information and be willing to alter their prescription writing habits in response to drug cost information. Physicians appear to be increasingly more receptive to the idea of incorporating price information into the decision process. In a study reported in 1954, physicians expressed little interest in considering price in the prescription decision process[4]. However, more recent evidence suggests that physicians will accept and use price information in a managed health care environment. In one study, providing drug price information to physicians in a managed care setting in a bulletin or newsletter format has been shown to reduce overall costs by as much as 30%[5].

The primary objective of this investigation was to develop an understanding of how an 'information' strategy would be accepted by physicians. To accomplish this objective we examined several basic questions. First, do physicians believe there is a need for accurate drug cost information and are they willing to use this information in prescribing decisions if it is provided? Next, what sources do physicians currently use for drug cost information and how satisfied are they with these sources? Lastly, are physicians willing to pay for drug cost information?

METHODOLOGY

A preliminary questionnaire was developed from an initial pool of items developed by the investigators. This was informally pretested on a small group of physicians resulting in some minor changes in phraseology. The final version of the instrument (Appendix A) contained three sections. The first section was a cover letter identifying the sponsor, voluntary nature and purpose of the study. The second section displayed a graph and tabular data of actual average prescription prices for the most frequently prescribed quantities of the top seven non-steroidal anti-inflammatory agents. The drug products included in the graph were selected based on dollar volume. The prices and quantities presented to the physicians were derived from a Medicaid database containing over 700,000 prescription charges for a one month period. The final section of the questionnaire contained the attitudinal items and several questions designed to assess physician's sources of and satisfaction with drug price information and to assess physician demographics. The three page questionnaire was printed, individually signed by one investigator and folded to fit into a first class business envelope. The instrument was designed so that after completion it could be easily re-folded exposing a business reply mail return address.

Two copies of a current mailing list composed of a random sample of 1,344 Georgia physicians were purchased commercially, facilitating an initial mailing and one follow-up ten days later. Surveys that were completed and returned were reduced into machine readable form, verified, uploaded to a central computer system and analyzed with the Statistical Analysis System[6].

RESULTS

The overall response rate to the survey was 22.6% with a total of 304 usable questionnaires being received. Two-thirds of the responding physicians reported that they practiced in a group practice setting. About one half (56.3%) had been in practice less than fifteen years and 43.8% were in practice for fifteen years or greater. The responding physicians were almost evenly divided between primary care (53.1%) and specialty (46.9%) practice.

Perceived Need for Drug Price Information

Physicians' responses to individual survey items indicated that there was significant need for drug cost information in medical practice. This is evidenced by the 82% of the physicians that indicated they needed more drug cost information than they currently received. Most of the responding physicians agreed that patients are concerned about drug costs (85%) and expect physicians to know about drug cost information (57%). Further, 59% of the respondents agreed that cost was a factor in patient compliance.

Use of Drug Price Information

Eighty-two percent of the physicians agreed that if they did know more about drug cost they could save their patients money on prescription drugs and 68% agreed that they would use drug cost information if it were more accessible. A total of 82% of the physicians agreed that health care administrators are concerned about drug prices. Eighty-seven percent of responding physicians indicated that they frequently use drug cost information in making prescribing decisions, however, 62% indicated that they believed cost should not be a consideration when choosing a drug therapy.

Drug Price Bulletin

A large majority of the respondents (90%) agreed that the newsletter concept was a good idea for providing physicians with drug cost information. However, only 46% indicated they would be willing to pay for information in this format. Physicians' willingness to pay for the service on an annual basis was categorized into $0, $0-$30, $31-$50, $51-$70, and more than $70. Only a few respondents indicated that they were willing to pay more than $30 per year for the service and, therefore, the item was dichotomized into those who expressed a willingness to pay something (46%) versus those who expressed no interest in paying for the service (54%).

Sources of Information and Satisfaction

Figures 1 and 2 show that physicians reported that they seek price information most frequently from patients, followed by pharmacists, pharmaceutical representatives, and lastly fellow medical practitioners. The survey results also indicated that physicians were most satisfied with the information received from patients and pharmacists and less satisfied with the information received from fellow practitioners and pharmaceutical representatives.

Physician Characteristics and Willingness to Pay

The results of the categorical analysis are represented in Table 1. This analysis produces a table similar to analysis of variance procedures with reported Chi Square values in place of the customary F ratios. The results indicated a significant relationship between the willingness to pay for the price information and the two variables years in practice and patient expectations. The interaction between the years in practice variable and the patient expectation variable proved not to be significant. No relationship was noted between willingness to pay for the prescription price information and physician specialty.

The individual effects of years in practice and patient expectations are reported in Figures 3 and 4. Those physicians who believed patients expect them to be knowledgeable about prescription prices were more willing to pay for the service. Also, those younger physicians who had been in practice for less than 15 years were more willing to pay.

DISCUSSION

Perceived Need for Drug Price Information

The results of this survey supported previous findings which indicated that physicians are poorly informed regarding prescription price information. Few medical practitioners stated that accurate drug price information was readily available to them in their practices. Physicians reported that they tend to rely upon and are satisfied with drug price information gathered from patients. However, drug price information received from patients should be interpreted cautiously. The information received from patient sources may be anecdotal, imprecise, or simply incorrect. Further, drug price information provided by patients cannot easily be organized in a manner which would allow the practitioner to compare similar products within a single therapeutic category.

The results of the survey also provided evidence to support a relationship between patients expecting their physician to be aware of drug price information and physicians willingness to pay for drug price information. Younger physicians also were found to be significantly more willing to pay something for a drug price information bulletin. This could be due to heightened sensitivity to patient expectations, since younger physicians would be at a stage in their career when they would be building a practice. Or, perhaps this is simply an artifact of society's recent movement toward cost containment in health care.

Feasibility of a Drug Price Bulletin

Based on the results of this study, an informational cost containment strategy for pharmaceuticals which relies upon voluntary subscriptions by physicians for drug price information should presently be approached cautiously. Physicians indicate they need accurate drug price information and that they will incorporate this into their decision process and prescription writing habits, providing an incentive to pursue this concept further. However, it was noted that many physicians were simply not willing to pay for this type of an information service. If it is assumed that willingness to pay for a service such as this is an indicator of perceived worth, these results indicate a general reluctance to support a drug price information service. However, as was noted above, physicians who are more sensitive to patient expectations, for example, younger physicians, are willing to pay for a drug price bulletin.

Considering recent trends in health care consumerism, and innovative patient behaviors such as "doctor shopping" where patients actively seek out a practitioner that will accommodate their needs and desires in a physician, the perceived worth of a drug price information should increase. The question still remains as to whether providing this information to physicians will have any impact on their prescription writing habits. A drug price information bulletin may be very effective in containing costs in managed care settings where savings can result in economic incentive for the physician. But what about fee-for-service physicians in private practice? The incentive for these professionals may be minimized because patient complaints may be deferred (for example, to pharmacists) and probably will not be directly assigned to the responsibility of the prescriber.

It seems that a drug price information service will most effectively impact on physician prescribing habits in situations which contain incentives for cost containment. For example, risk sharing contracts between physicians and managed health care provider groups might provide such an incentive. Arrangements such as these could limit prescription expense by passing a portion of the savings back to the physician which, in turn, would make price information necessary to attain financial objectives.

Physicians do perceive the need for drug price information, and realize that many patients may want them to be knowledgeable about prescription prices. However, is a general knowledge acceptable or do patients want physicians to be able to make specific price comparisons? Managed care and other cost containment strategies are on the rise. This certainly seems to provide an incentive for physicians to learn about drug prices. Fee for service physicians may currently have less incentive to be well informed about drug prices, however, as the increasingly cost conscious consumer begins to demand prescription price sensitivity from the physician, this too may change.

LIMITATIONS

This study was limited by the self reported nature of the data and the limited exposure physicians have to drug price information. Further the response rate was only approximately 23%, indicating that non-response bias could be a significant factor in this investigation. The results obtained could be biased since physicians which are more concerned about drug prices might be more likely to respond to a survey such as this. The low response rate and potential for bias are of great concern, however, this response rate should be sufficient to provide insight into this issue.

Table 1. Categorical Model Analysis of Willingness to Pay for Years in Practice and Patient Expectations of Price Knowledge

Source	DF	Chi Square	Probability
		Categorical Analysis	
Intercept	1	154.84	0.0001
Years In Practice[1]	1	5.17	0.0230
Patient Expectations[2]	2	12.23	0.0022
Interaction of Years in Practice and Patient Expectations	2	2.92	0.2323
Residual	0	0.00	1.0000

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[1] Less than 15 years in practice is coded "A" and 15 years or more is coded "B".

[2] Patients expect the physician to have prescription price information is coded "A" for agree, "D" for disagree, and "N" for neutral.

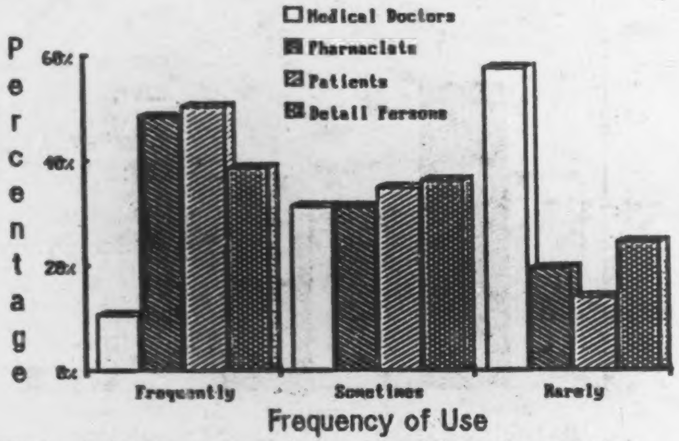

Figure 1. Sources of prescription price information and their frequency of use

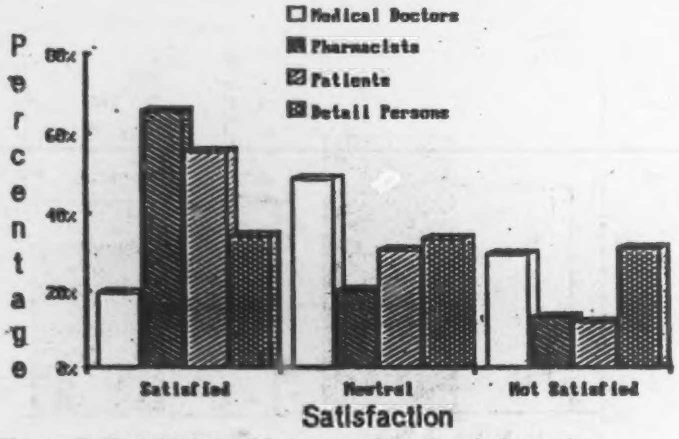

Figure 2. Satisfaction with sources, for prescription price information

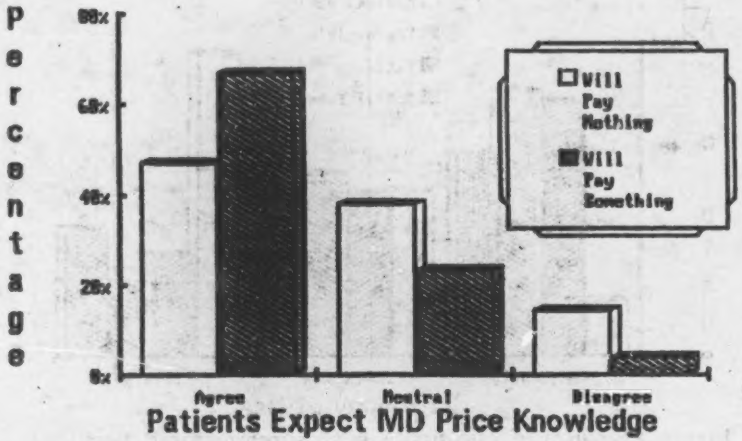

Figure 3. Perceived patient expectation for prescription price information knowledge

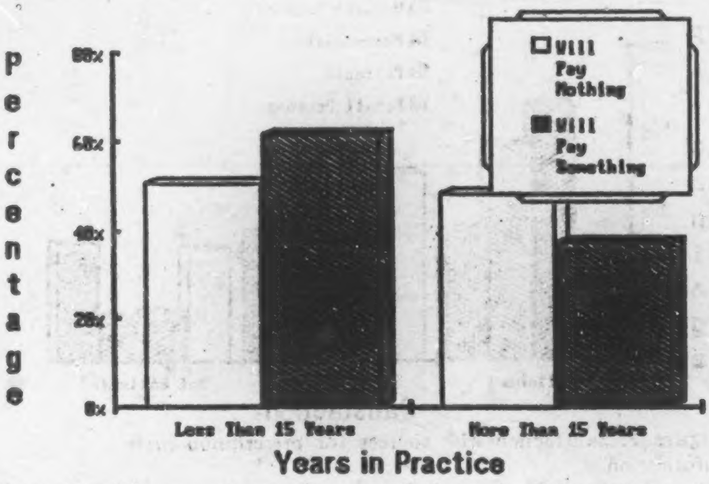

Figure 4. Willingness to pay for prescription price information and years in practice

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3. Oppenheim, G.L., Steven, H.E., Asworth, C., "The Family Physician's Knowledge of the Cost of Prescribed Drugs", *The Journal of Family Practice*, *12*, 1981, p. 1027-1030.

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5. Fendler, J.F., Gumbhir, A.K., and Sall, K., "The Impact of Drug Bulletins on Physician Prescribing Habits in a Health Maintenance Organization", *Drug Intelligence and Clinical Pharmacy*, *18*, 1984, p. 627-31.

6. SAS Institute, *SAS User's Guide*: *Statistics Version 5*, SAS Institute Inc., Cary, NC (1985).

Appendix A. Mail questionnaire sent to physicians.

The University of Georgia College of Pharmacy
Athens, Georgia 30602

February 8th, 1988

Dear Doctor:

Today's competitive health care environment requires attention to concerns that may have been less important in the past. One of these concerns is the cost of health care. We are particularly interested in the cost of one of your primary tools, prescription drugs.

The enclosed voluntary survey was designed to assess your feelings and needs regarding prescription drug cost information and will take only a few minutes of your time. You may be assured your responses are completely anonymous. The information we obtain will be helpful in developing effective methods of providing information on prescription drug costs to physicians.

The sample drug cost information enclosed within the survey was prepared from a database of over 700,000 actual prescription drug charges. This kind of information could be provided to physicians on a regular basis, for example, in a newsletter highlighting a different therapeutic category with each issue.

Prescription drug price information could save your patients money, something they are likely to appreciate. Please take just a few minutes to participate in this research project and complete the survey form. If you have questions or comments, please feel free to call (404) 542-7400 or write to the above address. Thank you.

Sincerely,

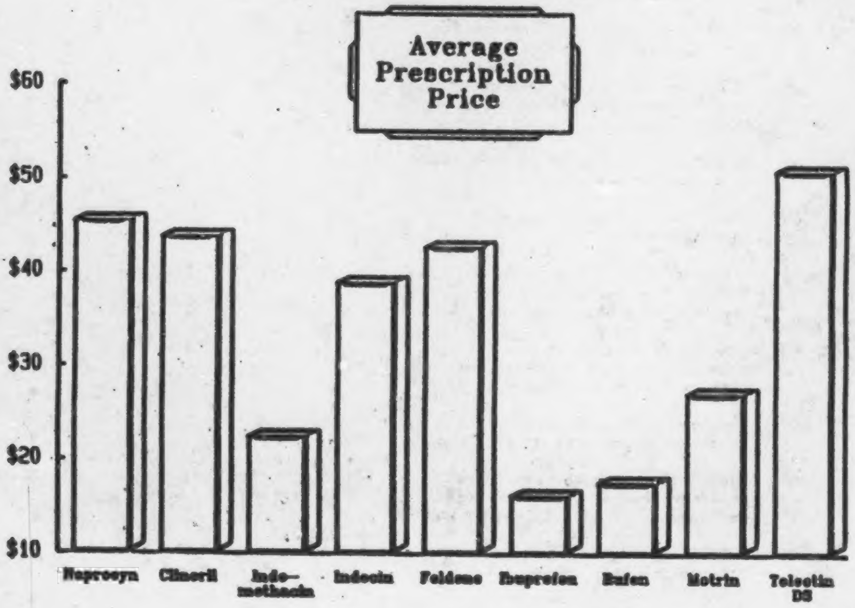
Jeffrey A. Kotzan

Jeffrey A. Kotzan, Ph.D.
Professor & Head
for Pharmacy Care Administration

Research at the University of Georgia involving human subjects is carried out under the oversight of the Institutional Review Board. Questions or problems regarding these activities may be directed to Dr. Piriou, Chairman, Institutional Review Board, Office of V.P. for Research, at the above address or by calling (404) 542-5941.

An Equal Opportunity/Affirmative Action Institution

Nonsteroidal Anti-Inflammatory Thirty Day Supply December, 1986



Trade Name	Generic Name	Usual 30 day Quantity	Average Price	Manufacturer
Naprosyn	naproxen	60	$45.36	Syntex
Clinoril	sulindac	60	$43.70	MSD
Indomethacin	indemethacin	90	$22.42	various
Indocin	indomethacin	90	$38.61	MSD
Feldene	piroxicam	30	$42.60	Pfizer
Ibuprofen	ibuprofen	90	$16.14	various
Rufen	ibuprofen	90	$17.58	Boots
Motrin	ibuprofen	90	$27.11	Upjohn
Tolectin DS	tolmetin sodium	90	$50.91	McNeil Pharm.

Physician Drug Cost Information Survey

Please indicate your level of agreement with the following statements:

	Strongly Disagree		Neutral		Strongly Agree
Q1. I need more drug cost information than I currently receive.	1	2	3	4	5
Q2. If I knew more about drug costs, I could save my patients money on prescription drugs.	1	2	3	4	5
Q3. My patients expect me to know about drug cost information.	1	2	3	4	5
Q4. I can easily obtain drug cost information.	1	2	3	4	5
Q5. Information comparing drug costs, such as that provided in the sample, would be a good idea.	1	2	3	4	5
Q6. I would be willing to pay for summary drug cost information similar to the sample provided.	1	2	3	4	5
Q7. The cost of drug therapy is an important concern to my patients.	1	2	3	4	5
Q8. The cost of drug therapy is an important concern to administrators, for example, in a hospital or HMO.	1	2	3	4	5
Q9. I frequently consider drug cost information when I make a prescribing decision.	1	2	3	4	5
Q10. If drug cost information were easier (more convenient, more accessible to me) to get, I would use it more frequently.	1	2	3	4	5
Q11. Information on drug costs should not be a factor in choosing a specific drug or brand of drug.	1	2	3	4	5
Q12. I believe drug cost is a major factor in patient non-compliance with prescribed medicines.	1	2	3	4	5

13. Please indicate HOW FREQUENTLY you use each of the following sources to obtain drug cost information:

	Always	Frequently	Sometimes	Rarely	Never
Colleagues (Physicians)	1	2	3	4	5
Pharmacists	1	2	3	4	5
Reference Source	1	2	3	4	5
Detail Person	1	2	3	4	5
Journal & Other Advertising	1	2	3	4	5
Feedback From Patients	1	2	3	4	5
Other Source (Specify: ______)	1	2	3	4	5

14. How satisfied are you with each of the following as sources of drug cost information?

	Very Satisfied		Neutral		Not Very Satisfied
Colleagues (Physicians)	1	2	3	4	5
Pharmacists	1	2	3	4	5
Reference Source	1	2	3	4	5
Detail Person	1	2	3	4	5
Journal & Other Advertising	1	2	3	4	5
Feedback From Patients	1	2	3	4	5
Other Source (Specify: ______)	1	2	3	4	5

15. How much would you be willing to pay to subscribe to a regular newsletter, providing information similar to that enclosed, highlighting a different therapeutic category each month?

1. Nothing
2. Less than $30 per year
3. $30 to $50 per year
4. $51 to $70 per year
5. More than $70 per year

16. What is your medical speciality? ______________________________

17. In what type of practice do you primarily work?

______ Solo
______ Group
______ Hospital only
______ HMO
______ Other

18. How many years have you been in practice? __________ years

19. In the space below, we welcome your comments or suggestions regarding how prescription drug cost information should be provided to physicians.

Thank you for your time. Please return by refolding the questionnaire with the return address on the outside, stapling or taping it shut, and dropping it in any mailbox - no postage is required.

NO POSTAGE
NECESSARY
IF MAILED
IN THE
UNITED STATES

BUSINESS REPLY MAIL
FIRST CLASS PERMIT NO. 559 ATHENS, GEORGIA

POSTAGE WILL BE PAID BY ADDRESSEE

COLLEGE OF PHARMACY
THE UNIVERSITY OF GEORGIA
ATHENS, GEORGIA 30602-9986

ATTENTION:

APPENDIX 5

DOCUMENTS PERTAINING TO KANSAS' DRUG PRICE NEGOTIATIONS

Medicaid programs

SKS

STATE OF KANSAS

DEPARTMENT OF ADMINISTRATION
Division of Purchases

MIKE HAYDEN,
Governor
NICHOLAS B. ROACH,
Director of Purchases

Landon State Office Building
900 Jackson
Room 102 N
Topeka Kansas 66612-1220
(913) 296-2376

Contract No. 27601

Date Mailed: March 14, 1988

Closing Date,
2:00 p.m., April 4, 1988

Contracting
Officer: Eileen Shaw, PPB

Telephone: (913) 296-3124

NOTICE TO BIDDERS

Invitations are hereby extended for bids on the attached proposed contract.

TYPE OF CONTRACT: Open End Contract XX Contract ______

ITEM: PHARMACEUTICALS: Medicaid/MediKan Program

AGENCIES: Department of Social and Rehabilitation Services, Topeka, KS

PERIOD OF CONTRACT: May 1, 1988 through April 30, 1989

GUARANTEE: None

Specifications and conditions for bidding and bid forms are attached. The signature page and bid form are to be completed and returned in the enclosed envelope not later than the closing date and time indicated. Inquiries relative to this proposal should indicate the contract number and be directed to the above Contracting Officer.

The State reserves the right to reject any or all proposals (bids) and to waive technicalities.

OPEN END CONTRACT: An Open End Contract shall be construed as a contractual agreement between a supplier and the State of Kansas to furnish an undetermined quantity of a commodity (or service) in a given period of time. This may be guided by an estimated quantity based on previous history or other means.

CONTRACT: A Contract shall be construed as a contractual agreement between a supplier and the State of Kansas to furnish a predetermined quantity of a commodity (or service) in a given period of time.

SPECIAL CONDITIONS
FOR PHARMACEUTICALS: MEDICAID/MEDIKAN PROGRAM

KANSAS DEPARTMENT OF SOCIAL AND REHABILITATION SERVICES

1. The Kansas Department of Social and Rehabilitation Services (SRS) intends to reduce the number of covered pharmaceuticals and to be more cost effective in providing awarded pharmaceuticals through this invitation for bid. The Special Conditions are intended to cover an agreement to adjust prices of specified "Pharmaceuticals" provided to eligible recipients of the Medicaid/MediKan Program administered by the Department of Social and Rehabilitation Services to a price designated as the bid price. The adjustment is the difference between the price paid by SRS to the retail pharmacy and the price submitted by the vendor in their bid response. For information, SRS is asking for bids only from manufacturers, and not from wholesalers. See number 10 on page 3.

   State of Kansas General Conditions and Instructions on Bidding shall be construed as part of these conditions.

2. Time of Letting: Sealed bids covering this proposal will be accepted for consideration until 2:00 p.m. on April 4, 1988 and at that time will be publicly opened.

3. Awards: Awards will be made, by each item, after all bids have been tabulated and each item given thorough consideration by the Drug Utilization Review (DUR) Committee. The DUR Committee will judge which product would be least expensive overall based on per diem use of the starred items at the price bid per unit. This should ensure a fair evaluation between drugs which are not identical. SRS reserves the right to award as a group like items and/or companion items and reserves the right to award on alternate bids.

4. Submitting Bids: Each bid shall be completed on one of the attached bid forms in accordance with the Instruction Sheet and submitted in the envelope provided herewith. The bidder shall identify his bid by inserting his name and address in the space provided on the outside of the envelope. The bid shall be delivered to the Department of Administration, Division of Purchases, Landon Building, Topeka, Kansas 66612, not later than the time scheduled for the opening of the bids.

5. Contract: The successful bidders will be required to enter into a written contract with the State of Kansas.

6. Prices: Only one may be quoted for each product offered, in the packaging (unit) closest to that given in the specifications attached. See "INSTRUCTION SHEET" for quoting more than one product for the same item of the specifications. Bid prices shall remain firm for the contract period.

7. Qualified or Conditional Bids: Vendor specified minimum order quantity conditions are considered conditional bids and are subject to rejection. Bids requiring multiple products or product lines as a condition of award will be rejected.

8. Quantities: The quantities indicated herein are estimated for the total period of the proposed contract. Estimates are based on usage by Medicaid/MediKan recipients. SRS reserves the right to reaward any drug product if the manufacturer fails to supply the estimated quantities. If estimated needs are greater or less than quoted, SRS assumes no responsibility to compensate the successful bidder for any difference in anticipated revenue.

9. Requirements and Specifications:

   (a) All products bid must conform to the specifications as designated herein.

   (b) All products for which bids are submitted must conform to the requirements of the specifications and formulae as designated herein; and where applicable must meet current standards of the U.S. Pharmacopeia, The Board of Health of the State of Kansas and/or its appropriate divisions and must be guaranteed as to meeting all requirements, regulations and comparison data as outlined in the Federal Food, Drug and Cosmetic Act and/or the Federal Food and Drug Administration. The manufacturer of products bid must have an FDA approved New Drug Application (NDA) or an approved abbreviated New Drug Application (ANDA).

(c) The Manufacturer's name and item stock number of the manufacturer or distributor must be shown on the bid sheets for each item whether bidding on specifications or an alternate; otherwise the bid will not be considered. All bids must indicate the actual manufacturer of that product on the bid response form provided. The State Division of Purchases must be informed in writing of any change in manufacturer during the contract period. Changes in manufacturer are subject to approval by the Drug Utilization Review Committee.

(d) The manufacturer/distributor certifies they are covered by a product liability insurance policy which includes provisions extending to the provider pharmacies and SRS.

(e) Awards will be made on the basis of one uniform brand product for all strengths or types of package specified for a particular dosage form.

10. Adjustment to Contract Payment: Provider pharmacies will continue to buy drugs and be reimbursed for Medicaid/MediKan prescriptions as usual. Adjustments (charge-backs) to the contract will be made by the manufacturer to SRS. A statement will be sent monthly from SRS to a successful bidder providing the following information:

(a) Units of each awarded drug dispensed.

(b) Amount reimbursed (by SRS) to pharmacies of each drug.

(c) Amount calculated at bid price of each drug.

(d) Amount owed to SRS (the difference between b and c) of each drug.

(e) Total amount owed to SRS (by the successful bidder).

(f) Time period covered.

(g) Year-to-date totals.

(h) Mailing address.

11. Identification of Payment: The manufacturer should identify the adjustment to contract payment by noting the contract number on the check.

12. Interest on Late Payments: Interest shall be charged on accounts that are 30 days overdue at the rate of 2% monthly.

13. Time Period Covered: Bid prices will be firm for one year. Successful bidders will be expected to make adjustments to the contract (in the form of payment to SRS) for Medicaid/MediKan prescriptions dispensed during that time. Adjustments (charge-backs) could be requested by SRS from an awarded vendor up to 6 months after contract period is ended based on previous dates of service which occurred during the contract period.

14. Container Size: Bids are being requested based on specific container sizes, but this is not intended to limit pharmacies to purchasing only that container size. An adjustment to the contract will be based on units dispensed and be independant from container size used by the pharmacy.

15. In the event no acceptable bids are received, SRS intends to select a single supplier for each described category based on current prices or to establish one price for each product.

16. Pre-Bid Conference: A Pre-Bid Conference will be held for potential bidders, beginning at 3:00 p.m. on March 23, 1988 in the Division of Purchases conference room on the 1st floor of the Landon State Office Building, 900 Jackson, Topeka, Kansas.

Attendance at the Pre-Bid Conference is not mandatory for vendors wishing to submit a bid, but all bidders are strongly encouraged to attend. Those interested in attending the conference should contact Eileen Shaw at (913) 296-3124 by Monday, March 21, 1988.

The purpose of this conference is to allow potential bidders to ask questions arising from their review of this bid proposal. Questions will not be allowed after the Pre-Bid Conference.

17. Questions Regarding the Implementation of this Contract: All questions regarding the implementation of this contract should be submitted to:

Katie Hauck, Administrator
Division of Medical Programs
Kansas Department of Social and
Rehabilitation Services
Docking State Office Building, 628-S
Topeka, KS 66612
(913) 296-3981

18. Questions Regarding the Requirements: SRS will accept questions concerning this bid proposal in writing prior to the Pre-Bid Conference. In addition, questions will be accepted at the Pre-Bid Conference. Questions that bear on substantial contractual issues will be answered in written form as an addendum to the bid proposal within five (5) working days after the conference. All organizations who received the bid proposal will receive the addendum. No questions may be submitted after the Pre-Bid Conference. Bidders shall not contact any SRS personnel regarding this bid proposal after the Pre-Bid Conference.

19. Addendum to the Bid Proposal: The state reserves the right to amend the bid proposal prior to the due date. If it becomes necessary to revise any part, an addendum shall be provided by certified mail to all potential bidders who have requested a copy. All bidders shall include acknowledgement of all addenda, as part of their bid quotation. Failure to acknowledge addenda may be grounds for disqualification of a bid quotation.

20. Termination of the Contract: SRS reserves the right to terminate this contract providing written notice has been given to the contractor at least thirty days prior to such proposed termination date.

21. Cost Liability: SRS assumes no responsibility and no liability for costs incurred by vendors prior to issuance of an agreement or contract.

PHARMACEUTICALS
INSTRUCTION SHEET

1. Enclosed are:
   1 copy Special Conditions for Pharmaceuticals: Medicaid/MediKan Program
   1 copy Bid Response Form and SRS Specifications for "Pharmaceuticals"
   1 pre-addressed envelope

2. Read Special Conditions and Specifications before making out bids.

3. The items listed on the combination Specifications and Bid Response Form are generally in alphabetical order. Please pay particular attention to the special conditions and instructions associated with all products for which bids are requested as a "therapeutic group" or "therapeutic drug class". Responses on these items must be made in the space associated with the appropriate generic name in the main listing.

4. Completing bid: All bid information must be typewritten. Make sure all information is legible. It is important that all instructions be followed accurately.

   a. Complete signature sheet by:
      1. Listing legal name of firm, telephone number, address, city, and state.
      2. Making sure form is signed and person signing indicates his title.

b. Complete bid form as follows:

1. Enter in this order: Brand name, manufacturer's name, manufacturer's catalog number, supplier's (bidder's) catalog number. Supplier's number alone or the use of "as specified" are not acceptable. If bidding an alternate product, list any deviations from Specifications.
2. Bid unit price only. Under the "packaging" column show what that unit is. The unit quoted should be that given in the Specifications or as close thereto as is available in the product bid. Awards can be made on units "approximating" those given in the Specifications.
3. On the additional blank forms provided, the bidder may offer two bids, one on a product designated in the Specifications for that item, and one on an alternate product, (not listed). (See paragraph 6 in the Special Conditions for bidding alternate products). For the purpose of establishing the total bid on the item, the high of the two bids shall be used.
4. Remove all pages "not bid". Return only those pages of the "Bid Form" having items quoted for bid.

5. Recheck signature page and make certain that all information is filled in and that it is SIGNED by an authorized person.

6. Please note the bid specifications contain two (2) alphabetized sections. The first section contains specifications for which awards will be made by therapeutic class. The second is the main body of pharmaceutical specifications for drug products. Every attempt possible has been made to accurately reflect the estimated usage for these pharmaceuticals.

7. Bids must be delivered to the Department of Administration, Division of Purchases, Landon State Office Building, Topeka, Kansas 66612, not later than 2:00 p.m., April 4, 1988.

Contract Proposal Number 27601

ITEM: PHARMACEUTICALS: Medicaid/MediKan Program - Dept. of Social & Rehab. Services

DEPARTMENT OF ADMINISTRATION
DIVISION OF PURCHASES
LANDON STATE OFFICE BUILDING
900 Jackson, Room 102 N
TOPEKA, KANSAS 66612-1220

SIGNATURE SHEET

Gentlemen:

We submit a proposal to furnish requirements during the contract period in accordance with the specifications and Schedule of Supplies.

LEGAL NAME OF PERSON, FIRM OR CORPORATION: ______

FIRM TELEPHONE NUMBER: AREA CODE ______ LOCAL NUMBER ______

ADDRESS: ______

CITY & STATE: ______ ZIP CODE ______

S. S. or FEIN Number ______

SIGNATURE: ______

TYPED NAME OF SIGNATURE: ______

TITLE: ______

DATE: ______

If awarded a contract and purchase orders are to be directed to an address other than above, indicate mailing address and telephone number below:

ADDRESS: ______

CITY & STATE: ______ ZIP CODE ______

TELEPHONE: AREA CODE ______ NUMBER ______

INFORMATION AND INSTRUCTIONS

This form is used to collect Small Business Procurement data. Therefore, it is necessary for the Certification Statement to be completed and the type of business be marked for each transaction.

TYPE OF BUSINESS (Please mark the appropriate box(es).

☐ SMALL	☐ OTHER THAN SMALL BUSINESS	☐ NON-PROFIT
☐ WOMEN-OWNED	☐ MINORITY	☐ HANDICAPPED

CERTIFICATION STATEMENT

KSA 1984 Supp. 75-6003 et. seq., Kansas Small Business Procurement Act states a business must meet the following requirements in order to be Certified and considered a small business.

(a) MUST BE A SMALL BUSINESS. "Small business" means a business which is independently owned and operated not dominant in its field of operation and is not an affiliate or division of a larger business.

(b) MUST BE A BUSINESS. "Business" means: (1) An entity organized for profit, including but not limited to, an individual, partnership, corporation, joint venture, association or cooperative; or (2) a bona fide nonprofit organization operating primarily for the habilitation, rehabilitation or employment of handicapped persons which employs at least five handicapped persons for every nonhandicapped person who is directly engaged in the manufacture and processing of products by the nonprofit organization.

(c) MUST NOT BE DOMINANT IN ITS FIELD OF OPERATION. "Dominant in its field of operation" means exercising a controlling or major influence in a kind of business activity in which a number of businesses are engaged. The following businesses shall be deemed dominant in their field of operation and, therefore, do not qualify as small business under this program: (1) Manufacturing businesses which employ more than fifty (50) persons and have in the preceding three (3) fiscal years exceeded three million dollars ($3,000,000) gross income annually; (2) General construction businesses which in the preceding three (3) fiscal years exceeded four million dollars ($4,000,000) gross income annually; (3) All other non-manufacturing businesses which employ more than twenty-five (25) persons and have in the preceding three (3) fiscal years exceeded one million five hundred thousand dollars ($1,500,000) gross income annually.

(d) MUST NOT BE AN AFFILIATE OR DIVISION OF A LARGER BUSINESS. "Affiliate or division of a larger business" means a business which is a subsidiary of or owned in part by a larger business which is dominant in its field of operation, or which is owned in excess of twenty percent (20%) by the partners, officers, directors, majority shareholders, or their equivalent, of a larger business which is dominant in its field of operation.

(e) MINORITY. "Minority person" means a citizen of the United States who is Negro, Hispanic, Oriental, American Indian, Eskimo, or Aleut.

(f) HANDICAPPED. "Handicapped person" means any person who: (1) Has a temporary or permanent physical disability that requires the use of a wheelchair, walker, braces or crutches; (2) Has temporarily or permanently lost the use of one or both legs; (3) Is determined and certified by a physician to be severely restricted in mobility, either temporarily or permanently, by a pulmonary or cardiovascular disability, arthritic condition or orthopedic or neurological impairment, (4) Is afflicted with or subject to any physical or mental impairment, or both, whether congenital or due to an injury, disease or illness of such character the impairment constitutes a handicap in obtaining employment or in retaining employment.

(g) MINORITY BUSINESS. "Minority business" means a business which more than 50% is owned by a minority person or persons.

(h) WOMEN-OWNED. "Women-owned business" means a business which more than 50% is owned by a woman or women.

I hereby certify that my business qualifies as a small business as per the foregoing requirements, and that my responses to the solicitation are accurate to the best of my knowledge.

Signature of Business Owner

Federal Tax I. D. No., or Soc. Sec. No.

Department of Administration
Division of Accounts and Reports
DA-146a (Rev. 1-81)

CONTRACTUAL PROVISIONS ATTACHMENT

Important: This form contains mandatory contract provisions and must be attached to or incorporated in all copies o any contractual agreement. If it is attached to the vendor/contractor's standard contract form, the that form must be altered to contain the following provision:

> "The provisions found in Contractual Provisions Attachment (form DA-146a), which is attached hereto and executed by the parties to this agreement, are hereby incorporated in this contract and made a part hereof."

The undersigned parties agree that the following provisions are hereby incorporated into the contract to which it i attached and made a part thereof, said contract being dated the ____ day of ______________, 19____.

1. TERMS HEREIN CONTROLLING PROVISIONS
It is expressly agreed that the terms of each and every provision in this attachment shall prevail and contro over the terms of any other conflicting provision in any other document relating to and a part of the contrac in which this attachment is incorporated.

2. AGREEMENT WITH KANSAS LAW
All contractual agreements shall be subject to, governed by, and construed according to the laws of the State o Kansas.

3. TERMINATION DUE TO LACK OF FUNDING APPROPRIATION
If, in the judgment of the Director of Accounts and Reports, State Department of Administration, sufficien funds are not appropriated to continue the function performed in this agreement and for the payment of th charges hereunder, State may terminate this agreement at the end of its current fiscal year. State agrees t give written notice of termination to contractor at least 30 days prior to the end of its current fiscal year and shall give such notice for a greater period prior to the end of such fiscal year as may be provided in th contract, except that such notice shall not be required prior to 90 days before the end of such fiscal yea Contractor shall have the right, at the end of such fiscal year, to take possession of any equipment provide State under the contract. State will pay to the contractor all regular contractual payments incurred throug the end of such fiscal year, plus contractual charges incidental to the return of any such equipment. Upo termination of the agreement by State, title to any such equipment shall revert to contractor at the end o State's current fiscal year. The termination of the contract pursuant to this paragraph shall not cause an penalty to be charged to the agency or the contractor.

4. DISCLAIMER OF LIABILITY
Neither the State of Kansas nor any agency thereof shall hold harmless or indemnify any contractor for an liability whatsoever.

5. ANTI-DISCRIMINATION CLAUSE
The contractor agrees: (a) to comply with the Kansas Act Against Discrimination (K.S.A. 44-1001 et seq.) and t not discriminate against any person who performs work hereunder, because of race, religion, color, sex, physica handicap unrelated to such person's ability to engage in this work, national origin or ancestry; (b) to includ in all solicitations or advertisements for employees, the phrase "equal opportunity employer"; (c) to compl with the reporting requirement set out at K.S.A. 1978 Supp. 44-1031; (d) to include those provisions in ever subcontract or purchase order so that they are binding upon such subcontractor or vendor; (e) that a failure t comply with the reporting requirements of (c) above or if the contractor is found guilty of any violation o such act by the Kansas Commission on Civil Rights, shall constitute a breach of the contract and it may be cancelled, terminated or suspended in whole or in part by the Director of Purchases, State Department of Administration.

Parties to this contract understand that subsections (b) through (e) of this paragraph number 5 are not applicable to a contractor who employs fewer than four employees or whose contract with this agency of the Kansas state government total less than $5,000 during this fiscal year.

6. ACCEPTANCE OF CONTRACT
This contract shall not be considered accepted, approved or otherwise effective until the statutorily required approvals and certifications have been given.

7. ARBITRATION, DAMAGES, WARRANTIES
Notwithstanding any language to the contrary, no interpretation shall be allowed to find the State or any agency thereof has agreed to binding arbitration, or the payment of damages or penalties upon the occurrence of a contingency. Further, the State of Kansas shall not agree to pay attorney fees and late payment charges; and no provision will be given effect which attempts to exclude, modify, disclaim or otherwise attempt to limit implied warranties of merchantability and fitness for a particular purpose.

8. REPRESENTATIVE'S AUTHORITY TO CONTRACT
By signing this document, the representative of the contractor thereby represents that such person is duly authorized by the contractor to execute this document on behalf of the contractor and that the contractor agrees to be bound by the provisions thereof.

9. RESPONSIBILITY FOR TAXES
The State of Kansas shall not be responsible for, nor indemnify a contractor for, any federal, state or local taxes which may be imposed or levied upon the subject matter of this contract.

10. INSURANCE
The State of Kansas shall not be required to purchase, any insurance against loss or damage to any personal property to which this contract relates, nor shall this contract require the state to establish a "self-insurance" fund to protect against any such loss or damage. Subject to the provisions of the Kansas Tort Claims Act (K.S.A. 1979 Supp. 75-6101 et seq.), the vendor or lessor shall bear the risk of any loss or damage to any personal property in which vendor or lessor holds title.

Vendor/Contractor:

________ ____________________
DATE Signature

____
Title

Agency Head/Authorized Representative:

________ ____________________
Date Signature

____
Title

STATE OF KANSAS

DIVISION OF PURCHASES

SRS Pharmaceuticals: Medicaid/MediKan Program

Product Specifications and
Bid Response Form

Table of Contents

		Pages
Section I:	Selected products for which awards will be made by therapeutic class	1 - 5
Section II:	Pharmaceutical specifications for other drug products	6

STATE OF KANSAS - DIVISION OF PURCHASES
BID RESPONSE FORM

VENDOR CODE

PAGE 1

CONTRACT: Pharmaceuticals: Medicaid/MediKan NO. 27601 PERIOD: From 5/1/88 Through 4/30/89

ITEM NO.	DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRI
	HISTAMINE H2 ANTAGONIST DRUG CLASS It is the State of Kansas' intent to obtain bids for the histamine H2 antagonists noted below. Product descriptions, strengths and package sizes are noted. The Drug Utilization Review (DUR) committee will review these items as therapeutic equivalents and reserves the right to award on a group basis for one brand based on bids submitted on the starred items.				
1.	Cimetidine 200mg tablets (Tagamet)	100 btl	920 btl		
2.	Cimetidine 300mg tablets	100 btl	14,700 btl		
3.	Cimetidine 400mg tablets	60 btl	7,000 btl		
4.	*Cimetidine 800mg tablets	30 btl	1,200 btl		
5.	Cimetidine 300mg/2ml Inj., 8ml vial	1 vial	120 vial		
6	Cimetidine 300mg/5ml Liquid	8 oz btl	925 btl		
7.	Ranitidine 150mg tablets (Zantac)	60 btl	30,000 btl		

STATE OF KANSAS - DIVISION OF PURCHASES
BID RESPONSE FORM

VENDOR CODE ☐

PAGE 2

CONTRACT: Pharmaceuticals: Medicaid/MediKan NO. 27601 PERIOD: From 5/1/88 Through 4/30/89

DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRICE
*Ranitidine 300mg tablets (Zantac)	30 btl	15,000 btl		
Ranitidine 25mg/ml Inj., 10ml vial	1 vial	120 vial		
Famotidine 20mg tablets (Pepcid)	30 btl	30,000 btl		
*Famotidine 40mg tablets	30 btl	15,000 btl		
Famotidine 10mg/ml Inj., 2ml vial	1 vial	100 vial		
Famotidine 10mg/ml Inj., 4ml vial	1 vial	150 vial		

STATE OF KANSAS - DIVISION OF PURCHASES
BID RESPONSE FORM

VENDOR CODE ☐

PAGE 3

CONTRACT: Pharmaceuticals: Medicaid/MediKan NO. 27601 PERIOD: From 5/1/88 Through 4/30/89

TEM NO.	DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRICE
	ORAL CEPHALOSPORIN DRUG CLASS is the State of Kansas' intent to obtain bids for the oral phalosporins noted below. Product descriptions, strengths d package sizes are noted. The Drug Utilization Review (DUR) mmittee will review these items as therapeutic equivalents d reserves the right to award on a group basis for one brand sed on bids submitted for 500mg capsules. phalexin (Keflex) or Cephradine (Anspor, Velosef)				
	Capsules: 250mg	100 cap/btl	2,700 btl		
	*Capsules: 500mg	100 cap/btl	1,800 btl		
	Oral Suspension: 125mg/5ml, 100ml btl	1 btl	2,600 btl		
	Oral Suspension: 250mg/5ml, 100ml btl	1 btl	4,500 btl		
	Oral Suspension: 500mg/5ml, 100ml btl	1 btl	100 btl		

STATE OF KANSAS - DIVISION OF PURCHASES
BID RESPONSE FORM

VENDOR CODE ☐

PAGE 4

CONTRACT: Pharmaceuticals: Medicaid/MediKan NO. 27601 PERIOD: From 5/1/88 Through 4/30/89

ITEM NO.	DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRIC
	HYDROCHLOROTHIAZIDE-TRIAMTERENE COMBINATIONS It is the State of Kansas' intent to obtain bids for the products noted below. Product descriptions, strengths and package sizes are noted. The Drug Utilization Review (DUR) committee will review these items as therapeutic equivalents and reserves the right to award on a group basis for one brand based on the bids submitted.				
19.	Capsules: 25mg of hydrochlorothiazide and 50mg of triamterene (Dyazide)	1,000 btl	1,100 btl		
20.	Tablets: 50mg of hydrochlorothiazide and 75mg of triamterene (Maxzide)	500 btl	2,200 btl		

STATE OF KANSAS - DIVISION OF PURCHASES
BID RESPONSE FORM

VENDOR CODE ☐

PAGE 5

CONTRACT: Pharmaceuticals: Medicaid/MediKan NO. 27601 PERIOD: From 5/1/88 Through 4/30/89

ITEM NO.	DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRI
	ALUMINUM HYDROXIDE, MAGNESIUM HYDROXIDE COMBINATIONS It is the State of Kansas' intent to obtain bids for the antacids noted below. Product descriptions, strengths and package sizes are noted. The Drug Utilization Review (DUR) committee will review these items and reserves the right to award on a group basis for one brand based on bids submitted on suspensions. Evaluation will be based on best dose per 15ml. Aluminum Hydroxide, Magnesium Hydroxide Combinations (Maalox, Aludrox, Delcid, Kolantyl, Maalox-TC, WinGel, others)				
21.	*Suspension	12 oz btl	62,500 btl		
22.	Tablets	100 btl	4,800 btl		

STATE OF KANSAS - DIVISION OF PURCHASES
BID RESPONSE FORM

VENDOR CODE ☐

PAGE 6

CONTRACT: Pharmaceuticals: Medicaid/MediKan NO. 27601 PERIOD: From 5/1/88 Through 4/30/89

TEM NO.	DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRICE
	GENERIC DRUG SPECIFICATIONS, SECTION II he Drug Utilization Review (DUR) committee reserves the ight to award on a group basis for one brand within a ategory based on bids submitted on the starred items.				
	luminum Hydroxide Gel (Amphojel)				
3.	*Suspension: 320mg/5ml	12 oz btl	2,275 btl		
4.	Suspension: 600mg/5ml	12 oz btl	1,750 btl		
	luminum Hydroxide, Magnesium Trisilicate, Alginic Acid, Sod. icarbonate Combination (Gaviscon, Gaviscon-II)				
.	*Tablets: Alum. Hydroxide 80mg, Magnesium Trisilicate 20mg, plus other ingredients	100 btl	3,000 btl		
.	Tablets: Alum. Hydroxide 160mg, Magnesium Trisilicate 40mg, plus other ingredients	48 btl	350 btl		

STATE OF KANSAS - DIVISION OF PURCHASES
BID RESPONSE FORM

VENDOR CODE ☐

PAGE 7

CONTRACT: Pharmaceuticals: Medicaid/MediKan   NO. 27601   PERIOD: From 5/1/88 Through 4/30/89

ITEM NO.	DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRIC
Artificial Tear Solutions (Isopto-Tears, Tears Plus, Tears Naturale, Soothe, others)					
27.	*Solution, ophthalmic: 15ml	1 btl	3,300 btl		
28.	Solution, ophthalmic: 30ml	1 btl	1,000 btl		
Griseofulvin Ultramicrosize (Fulvicin PG, GrisPEG)					
29.	Tablets: 125mg	100 btl	75 btl		
0.	*Tablets: 250mg	100 btl	140 btl		
1.	Tablets: 330mg	100 btl	55 btl		
etolazone (Diulo, Zaroxolyn)					
2.	*Tablets: 5mg	100 btl	580 btl		

STATE OF KANSAS - DIVISION OF PURCHASES
BID RESPONSE FORM

VENDOR CODE ☐

PAGE 8

CONTRACT: Pharmaceuticals: Medicaid/MediKan NO. 27601 PERIOD: From 5/1/88 Through 4/30/89

ITEM NO.	DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRI
Nifedipine (Procardia, Adalat)					
33.	*Capsules: 10mg	100 btl	10,300 btl		
34.	Capsules: 20mg	100 btl	100 btl		
Nitroglycerin Patches (Nitrodisc, Transderm-Nitro, Deponit, Nitro-Dur II)					
35.	Patch: 2.5mg/24hr	30 box	1,100 boxes		
—36.	*Patch: 5mg/24hr	30 box	7,000 boxes		
37.	Patch: 7.5mg/24hr	30 box	230 boxes		
38.	Patch: 10mg/24hr	30 box	3,700 boxes		
39.	Patch: 15mg/24hr	30 box	300 boxes		

STATE OF KANSAS - DIVISION OF PURCHASES
BID RESPONSE FORM

VENDOR CODE ☐

PAGE 9

CONTRACT: Pharmaceuticals: Medicaid/MediKan NO. 27601 PERIOD: From 5/1/88 Through 4/30/89

ITEM NO.	DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRICE
	Potassium Chloride (Slow-K)				
0.	Sustained release capsules 8meq	100 btl	5,600 btl		
1.	*Sustained release capsules 10meq	100 btl	4,300 btl		
2.	Sustained release tablets 8meq	100 btl	11,200 btl		
3.	*Sustained release tablets 10meq	100 btl	11,600 btl		

STATE OF KANSAS - DIVISION OF PURCHASES
BID RESPONSE FORM

VENDOR CODE ☐

PAGE 1

CONTRACT: Pharmaceuticals: Medicaid/MediKan NO. 27601 PERIOD: From 5/1/88 Through 4/30/89

ITEM NO.	DESCRIPTION	PACKAGING (correct if necessary)	ESTIMATED NEEDS	NDC NUMBER AND BRAND NAME YOU ARE BIDDING	BID PRI
Theophylline (Theo-Dur, SloPhyllin, Elixophyllin)					
44.	*Liquid: Elixir, Syrup or Solution 80mg/15ml	480mg/btl	100 btl		
45.	Sustained release capsules 125mg	100 btl	880 btl		
46.	*Sustained release capsules 250mg	100 btl	1,200 btl		
47.	Sustained release tablets 100mg	100 btl	550 btl		
48.	Sustained release tablets 200mg	100 btl	4,600 btl		
49.	*Sustained release tablets 300mg	100 btl	4,800 btl		

Contract Proposal No. 27601
Page No. A

STATE OF KANSAS

DIVISION OF PURCHASES

GENERAL CONDITIONS AND INSTRUCTIONS ON BIDDING

A. GENERAL CONDITIONS

1. **ACCEPTANCE OR REJECTION AND AWARD OF BID:** The State of Kansas reserves the right to accept or reject any or all bids or parts of bids, to waive any informality or technicality in bids, and unless otherwise specified to accept any item in the bid. In case of error in extension of prices or other errors in calculation, the unit price shall govern. Award will be made to the lowest responsible bidder complying with conditions and specifications of the invitation to bid.

2. **F. O. B. POINT:** Unless otherwise specified, all bids will be F.O.B. DESTINATION. This term shall mean delivered to a state agency's receiving dock or other designated point as specified in the request for bids.

3. **TAX:** Unless otherwise specified, bid prices should not include Federal Excise Tax, State Sales Tax or Transportation Tax. The State of Kansas shall not be responsible for, nor indemnify a contractor for, any federal, state or local taxes which may be imposed or levied upon the subject matter of State purchases or leases.

4. **BID AND PERFORMANCE GUARANTY:** The Director of Purchases is ~~authorized~~ by law to prescribe the amounts of deposit or bond, if required, to be submitted with a bid or a contract and the amount of bond, if required, to be given for the faithful performance of a contract.

   When a bid and/or performance guaranty is required, such requirements will be clearly outlined in the invitation to bid.

   Unless otherwise specified, the bid and performance guaranty must be:
   (a) Certified or cashier's check, or

   (b) A Bid and Performance Bond (this form furnished upon request) payable to the State of Kansas. The Bid and Performance Bond must be filed with and approved by the Director of Purchases of Kansas prior to closing date of any quotation for which such bond is to serve as guaranty.

5. **RETURN OF GUARANTY:** The guaranty of the successful bidder will be returned after the contract has been completed by delivery and acceptance of, and payment for goods and/or services. The guaranty of the unsuccessful bidder will be returned after an award has been made to the successful bidder.

6. **LIQUIDATED DAMAGES:** If the successful bidder fails or refuses to enter into a contract or fails to provide goods and/or services in accordance with terms and conditions of an accepted bid, then the State of Kansas may require forfeiture of the guaranty as liquidated damages and/or removal from the bid list.

7. **DEFAULT:** Any vendor who defaults on delivery as defined in the proposal form may, at discretion of State, be barred from bidding for a period to be determined by the State.

8. **NEW MATERIALS, SUPPLIES OR EQUIPMENT:** Unless otherwise specified, all materials, supplies or equipment offered by a bidder shall be new, unused or of recent manufacture, first class in every respect, and suitable for their intended purpose; also, all equipment shall be assembled and fully serviced, ready for operation when delivered.

9. **INSPECTION:** The State reserves the right to reject, upon arrival at destination, any items which do not conform with specifications under which they were purchased. Sampling and inspection may be made on items at source of supply. Suppliers may ask for an inspection of goods at point of manufacture; however, such inspection will be made for convenience of the supplier, and the State reserves the right for final acceptance or rejection at point of delivery.

10. PATENTS: The seller shall protect the State from any and all damages or liability arising from alleged infringements of patents.

11. COMPLIANCE WITH KANSAS ACT AGAINST DISCRIMINATION: All bidders must agree and covenant as a condition of contract that they will comply, if required by law, with provisions of K.S.A. 44-1030 et seq. and will observe provisions of the Kansas Act Against Discrimination.

12. INSURANCE: The State of Kansas shall not be required to purchase any insurance against loss or damage to any personal property, nor shall the state establish a "self-insurance" fund to protect against any such loss or damage. Subject to the provisions of the Kansas Tort Claims Act (K.S.A. 1979 Supp. 75-6101 et seq.), the vendor or lessor shall bear the risk of any loss or damage to any personal property in which vendor or lessor holds title.

13. PUBLIC RECORDS: A complete public record file of each bid transaction is maintained for at least five (5) years by the Division of Purchases. After a bid is awarded and filed, the file is available for review by interested parties during regular business hours.

B. GENERAL INSTRUCTIONS TO BIDDERS

1. BID FORMS OR REQUEST FOR QUOTATION: Bids should be submitted only on forms provided by the State. The bid must be received in the office of the Division of Purchases not later than the date and time scheduled for closing of the bid.

2. EQUIVALENT BIDS: When brand names or trade names and model numbers followed by the words "or equivalent", or "or approved equal" are used in the bid invitation, it is for the purpose of item identification and to establish standards for quality, style and features. Bids on equivalent items of substantially the same quality, style and features are invited. However, to receive consideration, such equivalent bids must be accompanied by sufficient descriptive literature and/or specifications to clearly identify the units and provide for competitive evaluation.

3. ACCEPTANCE OF BIDS: Bids are invited on the basis that acceptance of the offer to furnish articles as described in the invitation shall constitute a contract between the bidder and the State of Kansas, which will bind the bidder to furnish and deliver articles for which the offer is accepted. If specifications and contents of the proposal cannot be complied with, a bidder may elect not to bid.

4. SAMPLES: Samples of items when required, must be furnished at no expense to the State; and, if not destroyed in the evaluation or testing process, will be returned at bidder's expense, if requested.

5. UNIT PRICES: Prices must be stated in units of quantity specified.

6. DISCOUNT: All offered discounts will be considered in determining the low bid.

7. PREPARATION OF BID: Each bid must be legible and properly signed. Prices are to be entered in spaces provided on the bid form. Mathematical extensions and totals shall be indicated where required. In cases of errors in extensions or totals, the unit price will govern.

8. SIGNATURE OF BIDS: Each bid must give the complete mailing address of bidder and be signed by him with his legal signature. Bids by partnerships must be signed by one of the members of the partnership or by an authorized representative. Bids by corporations must be signed in the name of the corporation followed by signature and title of the president, secretary, or other person authorized to bind it in the matter. The names of all persons signing should be typed or printed below the signature.

9. MARKING AND MAILING BIDS: Bids must be securely sealed in envelopes provided or other suitable envelopes addressed and marked on the outside as required by the invitation, including name and address of bidder, quotation number and closing date. Telegraphic or telephone bids are not acceptable unless specifically provided for in the bid invitation.

10. TIME FOR RECEIVING BIDS: All bidding will close promptly at 2:00 p.m. Central Standard or Daylight Savings Time, whichever is in effect at Topeka, Kansas, or other designated bid opening site on the date specified in the invitation to bid. Formal bids received prior to time of closing will be securely kept, unopened until closing time. The State will accept no responsibility for prematurely opening of a bid not properly identified on outside of envelope as requested.

11. MODIFICATION OF BIDS: Telegraphic or written modifications of bids already submitted will be accepted by the Division of Purchases if received prior to the date and hour scheduled for closing of bids.

12. WITHDRAWAL OF BIDS: A bid may be withdrawn on written, telegraph or personal request received from a properly identified bidder prior to the date and hour scheduled for closing of bids.

13. BIDDERS PRESENT: At the date and hour scheduled for closing, bid prices will be made public for information of interested bidders who may be present either in person or by representative. Such information is not to be construed as meaning low bidder has met all specifications as set out in invitation to bid.

14. CAUSE FOR BID REJECTION: Any bid may be rejected for justifiable reason, including but not limited to the following:

    (a) Failure of bidder to sign bid form.

    (b) Irregularities of any kind.

    (c) Alteration of bid form.

    (d) Obvious errors on part of the bidder.

    (e) Failure to submit required bid guaranty.

    (f) Failure to furnish requested pricing or other information.

    (g) Submission of a late bid.

    (h) Offering of alternates not called for in the invitation to bid.

    (i) Failure to comply with F.O.B. requirements.

15. NOTICE OF AWARD: Depending upon the type of purchase transaction, the Division of Purchases issues either a Purchase Order or a Contract to successful bidders.

16. CHANGES: Changes in any request for quotation, purchase order or contract may be made only upon written approval from the Director of Purchases.

17. INVOICES AND PAYMENTS: After furnishing acceptable goods or services, vendors may obtain payment by presenting invoices to the receiving state agency.

18. DA146a: Kansas Contractual Provisions Attachment, Form DA146a attached, must be signed and is made a part of this contract.

NOTE: Bidders should be aware that the various state agencies (Departments, Boards, Commissions, Institutions, etc.) have delegated authority for making certain small purchases of goods and services, and all opportunities to bid do not originate in the Division of Purchases.

Bids with an estimated value in excess of $10,000.00 are advertised in the Kansas Register. Interested bidders may contact Kansas Register, Secretary of State, State Capitol, Topeka, Kansas, 66612 for subscription information.

July, 1987

MSD
MERCK
SHARP &
DOHME

DIVISION OF MERCK & CO., INC., WEST POINT, PENNSYLVANIA 19486

March 23, 1988

Ms. Eileen Shaw, PPB
Division of Purchases
State of Kansas
Landon State Office Building
900 Jackson - Room 102 N
Topeka, Kansas 66612-1220

Reference: Your Contract No. 27601
MSD Bid No. 88-3052

Dear Ms. Shaw:

We are in receipt of your request for Bid opening April 4, 1988. The conditions of sale are listed under the attached General Information section.

We note the Bid contains requirements for PEPCID® which we will be pleased to quote as follows:

PEPCID®	20mg tabs, 30/btl	MSD Prod. No. 3535-30	$ 24.53/btl
	40mg tabs, 30/btl	MSD Prod. No. 3536-30	47.41/btl
PEPCID®	I.V., 20mg/2-mL Single-Dose vl, 10/bx	MSD Prod. No.3539-04	47.50/bx
PEPCID®	I.V., 20 mg/2-mL Two-Dose vial (Must be purchased in multiples of 5 vls)	MSD Prod. No.3541-14	7.36/vl

TERMS: 2%, 15th proximo from date of invoice
DELIVERY: Prompt, As Required
F.O.B.: Destination
PERIOD: Prices for the above items are firm for the period 5/1/88 to 4/30/89

With regard to the reimbursement program, our prices are for direct shipment and billing to the State of Kansas agencies and institutions only. It has not been our policy to allow rebates, service fees, or chargebacks of any kind.

M

MARION LABORATORIES, INC.

P.O. BOX 8480 • KANSAS CITY, MISSOURI 64114-0480 • 816-966-4000

March 30, 1988

State of Kansas
Department of Administration
Division of Purchases
Landon State Office Bldg.
Topeka, KS 66612

Attention: Ms. Eileen Shaw, PPB

Dear Ms. Shaw:

We have received your invitation to offer quotations on our product GAVISCON®.

We will be unable to offer a quotation at this time, since our current bid policies preclude our offering quotations for "third-party pay" programs.

Thank you for contacting us.

Sincerely,

MARION LABORATORIES, INC.

Alfred A. Mannino
Vice President
Corporate Affairs

JDT/rk
Enclosure

388/116

ABBOTT

Hospital Products Division

Abbott Laboratories
Abbott Park, Illinois 60064

March 25, 1987

State of Kansas
Department of Administration
Division of Purchases
900 Jackson Room 102 N
Topeka, KS 66612-1573

RE: Bid 27601-A

Dear Sirs:

The enclosed request for quotation is being returned because we are not in a position to quote at this time.

We appreciate your consideration in listing Abbott Laboratories as an acceptable vendor and ask that we be maintained as an eligible bidder for future requests.

Sincerely,

Meredith E. Durant

Meredith E. Durant
Manager, Contract Pricing

MED/ djn

Enclosure

A. H. Robins Company
1407 Cummings Drive
P. O. Box 26609
Richmond, Virginia 23261-6609
Cable Robinco/TWX 7109560001
Telephone (804) 257-2000

A·H·ROBINS

Eileen Shaw, PPB
Contracting Officer
Department of Administration
Division of Purchases
900 Jackson RM 102 N
Topeka, KS 66612-1573

Dear Ms. Shaw

March 28, 1988

This is to acknowledge receipt of the invitation to bid for the Medicaid/MediKan Program.

We respectfully must decline this invitation.

Thank you for including us. Please continue to keep us on your bidding list.

Cordially,

Laurie Metzger

Laurie Metzger
Bid & Contract Administration

McNEIL
PHARMACEUTICAL

SPRING HOUSE, PA 19477-0776 (215)628-5000

April 3, 1987

STATE OF KANSAS
Topeka, KS 66612

RE: Bid#27601 A DUE: 4/15/87

Gentlemen:

There are no items on this particular bid on which we can submit prices.

However, please do not remove our name from your list, since we will bid as competitive items appear.

Thank you for your cooperation.

Sincerely,

Jim A. Bush, Manager
Bids and Contracts

JAB/

STATE OF KANSAS

DEPARTMENT OF ADMINISTRATION
Division of Purchases

4/15/87

MIKE HAYDEN,
Governor
NICHOLAS B. ROACH,
Director of Purchases

Landon State Office Building
900 Jackson
Room 102 N
Topeka, Kansas 66612-1220
(913) 296-2376

"NO BID"

GENEVA GENERICS, INC.

Joseph A. Hebda
Contract Manager

4/6/87
Date

Contract No. 27601-A

Date Mailed: March 18, 1987

Closing Date, 2:00 p.m., April 15, 1987

Contracting Officer: Eileen Shaw, PPB

Telephone: (913) 296-3124

NOTICE TO BIDDERS

Invitations are hereby extended for bids on the attached proposed contract.

TYPE OF CONTRACT: Open End Contract XX Contract ______

ITEM: PHARMACEUTICALS/SOCIAL & REHABILITATION SERVICES

AGENCIES: Department of Social & Rehabilitation Services, Topeka, KS

PERIOD OF CONTRACT: May 1, 1987 through April 30, 1988

GUARANTEE: None

Specifications and conditions for bidding and bid forms are attached. The signature page and bid form are to be completed and returned in the enclosed envelope not later than the closing date and time indicated. Inquiries relative to this proposal should indicate the contract number and be directed to the above Contracting Officer.

The State reserves the right to reject any or all proposals (bids) and to waive technicalities.

OPEN END CONTRACT: An Open End Contract shall be construed as a contractual agreement between a supplier and the State of Kansas to furnish an undetermined quantity of a commodity (or service) in a given period of time. This may be guided by an estimated quantity based on previous history or other means.

CONTRACT: A Contract shall be construed as a contractual agreement between a supplier and the State of Kansas to furnish a predetermined quantity of a commodity (or service) in a given period of time.

FYI
Pete

cc Adm Cons Rehab [illegible]

Ad Stf

Gerald J. Mossinghoff
PRESIDENT

Pharmaceutical
Manufacturers
Association

MEDICAL PROGRAMS
APR 30 11 07 AM '87
SRS
RECEIVED

April 24, 1987

The Honorable Michael Hayden
Governor
State of Kansas
State Capitol, 2nd Floor
Topeka, Kansas 66612

Dear Governor Hayden:

The Pharmaceutical Manufacturers Association (PMA) represents over 100 major firms engaged in the research and development of prescription drugs. PMA recognizes the difficult situation you presently confront in seeking to deal with the state's current budgetary shortfall, while providing quality health care to the state's Medicaid patients. However, we wish to raise a number of concerns about recent cost-containment actions and proposals affecting Medicaid pharmacy services which are being implemented by Dr. Harder, Secretary of the Department of Social and Rehabilitation Services.

These proposals include (1) the establishment of a very restricted drug formulary, (2) the adoption of state MACs on various drug products, and (3) the implementation of competitive bidding to limit drug coverage to selected products within a drug class. PMA believes that these proposals represent unsound cost-containment policies that will have adverse consequences on patient care and on the overall operation of an extremely cost-effective pharmacy program. We have notified Secretary Harder of our concerns regarding these measures and have received an unsatisfactory response to date (see enclosed correspondence).

In addition to the adverse medical and economic consequences of these proposals, we believe there are serious legal issues specifically associated with the competitive bid/rebate program. Our analysis points to a number of important questions regarding the legal basis of this program:

1. What is the state's statutory authority for instituting the competitive bid/rebate program?
2. What is the state's statutory authority for applying the competitive bid/rebate program to sole-source pharmaceutical products?

3. What is the state's position on the applicability of the federal Medicaid Fraud and Abuse Act to payments made under the competitive bid/rebate program? This Act makes it a crime to give or receive rebates for Medicaid-reimbursable items, 42 U.S.C.A. Section 1395nn(b). This question is currently being reviewed by the federal Health Care Financing Administration.

4. Does the state's acceptance of rebates violate the Robinson-Patman Act's prohibition against knowingly inducing or receiving discriminatory prices, 15 U.S.C. 13(f)?

5. Was the Kansas Medical Care Advisory Committee consulted on formulary changes and implementation of the competitive bid/rebate program as required by 42 C.F.R. Section 431.12?

6. Would individual recipients be given prior notice and opportunity for a hearing before their benefits were reduced through implementation of the competitive bid/rebate program?

Given the major importance of these questions to both Medicaid patients and providers, we respectfully request that you direct the Department of Social and Rehabilitation Services to cease implementation of the competitive bid/rebate program until the State addresses these significant legal issues.

Sincerely,

Gerald J. Mossinghoff

Enclosure

cc: Dr. Robert C. Harder
Secretary
Department of Social and
Rehabilitation Services
Mr. Peter Rinn
Legal Department
Department of Social and
Rehabilitation Services

To Winston
FYI
[illegible]
3/2

3/16 39
10 LKK

William M. Henry
Attorney at Law
627 S. Topeka, P.O. Box 477
Topeka, Kansas 66601
Telephone (913) 233-[illegible]

KANSAS SOCIAL AND
REHABILITATION SERVICES
MAR 3 1988
OFFICE OF THE
SECRETARY

February 29, 1988

Governor Mike Hayden
State Capitol
Topeka, Kansas 66612

Dear Governor:

On behalf of my client, the Pharmaceutical Manufacturers Association, I wish to share with you that Association's view on a problem with a proposed action by the Department of Social and Rehabilitation Services.

Member companies of PMA and myself have already discussed this issue with Winston Barton. We appreciate the time and attention he gave us. We also appreciate the forthright manner of Mr. Barton in expressing his intentions and plan of action. The Secretary was kind enough to tell us he would be discussing this issue with you this week and I would like to share my client's position.

The Secretary has told us he plans to utilize a bid/rebate program that he would utilize in the future on selected single-source prescription drugs.

Mr. Barton told me that his department intends in the future to ask pharmaceutical manufacturers to submit "bids" on selected prescription products.

The medical services staff of SRS believes that by bidding for a single prescription drug, the department would save the state Medicaid funds.

Single-source pharmaceuticals are drugs for which pharmaceutical manufacturers hold patents. On an industry average only about one of every ten thousand chemical compounds is actually ever introduced as a new product. It generally takes from seven to ten years after discovery of new compounds for a company to gain approval by the Federal Food and Drug Administration to market the new products and this research and development time averages in cost from $91-100 million.

Secondly, each of these pharmaceutical drugs is unique and is designed for different treatment regimens. It is extremely difficult to find drugs that are so similar in nature and treatment regimens as to be able to substitute these drugs appropriately.

Last year the medical services division of SRS attempted to try this procedure with a group of anti-ulcer drugs, commonly referred to as H-2 antagonists. The Department sought bids from the manufacturers of these prescription drugs but received none. The Department then arbitrarily picked a single anti-ulcer drug and delisted other H-2 antagonists from the formula list. The cost savings from this move never occurred. In fact, the Department is now paying more for the single anti-ulcer drug than it was paying previously when three different anti-ulcer drugs were available.

In addition, the Department's Drug Utilization Review Committee (which is made up of Kansas physicians, pharmacists, and nurses) has recommended that these anti-ulcer drugs be reinstated to the formula list of Medicaid. The Department's Special Consultant in Pharmacology also recommended that this action be reversed and the drugs restored to the formula list. Despite these recomendations and other comments from well-known Kansas physicians, the medical staff has refused to do so.

During the past year, representatives of the manufacturers pharmaceutical association companies have been meeting with the staff of SRS and have offered to work in establishing treatment regimens and procedures to see that certain overdosages and overprescribing could be eliminated. Despite offers of help from the companies, the Department has refused to cooperate to help in these cost-cutting areas.

I cannot speak of course for every individual member of the 120 pharmaceutical research manufacturing firms that compose the membership of PMA, but I suspect if Secretary Barton does seek bids for these types of pharmaceutical products in the future he will probably receive none. The reason for this lack of response is that each company has a tremendous amount of research and development costs wrapped up in these particular drugs. The active life of a prescription pharmaceutical usually only lasts patent wise for seven years. When the patent goes off any generic facsimile can be produced by anyone at that time. As a result each company has a narrow window in which they can recover their research and development costs with a given product.

Other states have made attempts to set up a similar system in the past, including the state of California. However, the difficulty in comparing each pharmaceutical product to another is extremely complicated. In addition, the administrative costs in arriving at the "best" common treatment drug are high.

There is a legal problem as well in this area. Any so called "refund or rebate" returned to the state would have to be shared with the Federal Medicaid Program. Frankly, since there may well be no bids offered in this situation this problem may not occur because the state will have no savings to share with the federal government and Medicaid.

More serious, however, is the effect that the competive bidding proposal at issue could have on the quality of health care services provided to recipients under the Medicaid program. If it is not economically feasible for pharmaceutical manufacturers to supply drug products at a reduced price, these products will probably be eliminated from Medicaid coverage. What occurs in this instance is that the Kansas Medicaid Pharmacy Program would be structured on the basis of marketing decisions of individual manufacturers rather than on the basis of rational considerations regarding the necessary and appropriate drug therapy for the clients of SRS.

The final irony in this particular situation is that for more than a year now, members of the Pharmaceutical Manufacturers Association have been meeting with the medical assistance staff of SRS attempting to cooperate and establish new techniques and regimens to reduce costs incurred by Medicaid in the disposition of certain medical products.

Despite the efforts of the industry, members of the staff of SRS have refused to go forward with these possible cost saving measures and have instead chosen the bid-rebate program which has proven to not produce any savings and in effect limits physicians in Kansas from utilizing all possible pharmaceutical treatments that could reduce hospitalizations and other treatments that are far more expensive.

I, or representatives of any of our member companies, would be most willing to meet with you to discuss in detail this issue at your convenience. Thank you for your consideration of this issue and we are at your call for any further information in this area.

Very Truly Yours,

Bill

William M. Henry
Attorney-at-Law

WMH/ss

cc: Woodrow Allen, Vice President Government and State Affairs, PMA
William A. Dean, Midwest Government Affairs Manager, Merrill Dow Pharmaceuticals, Inc.

Merrell Dow

William A. Dean
MERRELL DOW PHARMACEUTICALS INC.
Midwest Government Affairs Manager
8304 Connell Drive
Overland Park, Kansas 66212

MERRELL DOW PHARMACEUTICALS INC.
Subsidiary of The Dow Chemical Company
P.O. Box 429553
Cincinnati, Ohio 45242-0553, U.S.A.
Telephone: (513) 948-9111
Telex: 214320

KANSAS

Oct. 24, 1988

CODE: KSPMATF

Gene A. Appel, Hoechst
John Stockton, Schering
Bill Henry, KS. PMA
Carl Dahl, Robins
Oren Dougherty, Lilly
Bill Durr, Ciba-Geigy
Kurt Furst, Pfizer
Allen Farkas, Beechan

Jack Graham, Glaxo
Bill Howell, Upjohn
Frank Jackson, Squibb
Bert Jones, B-W
Tom Joy, MSD
Lon Lowrey, Sandoz
Bill Dean, Merrell Dow

Lois Moran, SKF
Myrle Myers, Lederle
Jean Neal, Roche
Tom Rickman, Marion
Paula Duhaime, PMA
Dave Schreier, Rorer
Mike Wright, Syntex
Bill Yates, KPhA

The Kansas PMA Task Force Steering Committee which was formed at the St.Louis PMA Region VI Meeting made a presentation at the Kansas Legislative PH&W Interim Committee Hearing on Friday, October 21, 1988. It went very well.

We presented the enclosed overview of the Drug Vendor Program,"Cornerstone of A Cost-Effective Medicaid Program." The Executive Summary is attached for your review. Myrle Myers, Lederle GAM, presented the review of five multi-source products which were on the Bid-Rebate Proposal. She showed the cmte how placing a MAC on four of them would save the State of Kansas over $110,000. vs the Bid-Rebate proposal. Lois Moran presented an overview of single source products and a recap of the H-2's, costs and utilization with no savings to SRS by selecting one of the H-2's for the Medicaid Formulary. Bill Henry recapped our program. Complete hand-outs, overhead visuals, pamphlets, etc. were presented to each legislator.

KPhA Executive Director Bob Williams supported our position that drugs are cost effective. Harold Rhiem, Executive Director of the Osteopathic Assn. also spoke supporting our position.

Katie Klassen and Gene Stephens of SRS rebutted some of the points made with off the cuff presentations. Their responses were inadequate for committee members, who asked pertinent questions. They made points for us.

We followed up with letters restating our position on a non-restrictive drug formulary which is cost effective. We are also rebutting Klassen's remarks that no recommendations on adding all H-2's back to the formulary.

As soon as we get feedback from the various PH&W Committee Members, we shall complete further plans to take action to get a non-restrictive formulary. We welcome any and all suggestions and comments. Please send to William M. Henry, Attorney At Law, PMA Kansas Counsel, P. O. Box 477, Topeka, KS. 66601.

Our Legislative B-B-Q is a "GO" situation. We have March 21, 1989 blocked off for our Legislative function with the Legislative Services Agency. We have space reserved at the ExpoCentre Heritage Hall, 23rd & S. Topeka Blvd., Topeka. We have arrangements with Senator Gene Anderson to provide us with food, drink and good cheer. Please block March 21, 1989 in your books.

Bill
Bill Dean

Myrle
Myrle Myers

cc

KANSAS SOCIAL AND
REHABILITATION SERVICES

JUN 15 1989

OFFICE OF THE
SECRETARY

STATE OF KANSAS

OFFICE OF THE ATTORNEY GENERAL

2ND FLOOR, KANSAS JUDICIAL CENTER, TOPEKA 66612-1597

ROBERT T. STEPHAN
ATTORNEY GENERAL

MAIN PHONE: (913) 296-2215
CONSUMER PROTECTION: 296-3751
TELECOPIER: 296-6296

June 14, 1989

ATTORNEY GENERAL OPINION NO. 89-74

Winston Barton, Secretary
Social and Rehabilitation Services
Docking State Office Bldg., 6th Floor
Topeka, Kansas 66612

RE: Commerce and Trade -- Monopolies and Combinations in Restraint of Trade -- Discrimination in Price; Discrimination; State Drug Bidding Program; Participation by Other States

Monopolies and Unfair Trade -- Restraint of Trade; General Provisions -- Unfair Trade

Synopsis: Although the proposed drug bid program raises serious antitrust questions, it is our opinion that it does not represent a per se violation of antitrust laws. Under a rule of reason analysis the proposed bid program may survive an antitrust challenge. The proposed program should be conducted in a manner that renders the market more, rather than less, competitive and does not allow one manufacturer to unlawfully possess market power to the exclusion of its competitors. Cited herein: 15 U.S.C. § 1-27.

* * *

Dear Secretary Barton:

You request our opinion concerning a proposed pharmaceutical bid program and extension of that bid program to other states wishing to participate. You specifically ask whether the bid process and the extension of the process to other states violates antitrust laws.

Pursuant to conversations with and correspondence from the Department of Social and Rehabilitation Services (SRS) and its legal staff, we understand that the bid process works as follows: SRS solicits and accepts separate bids on each of certain specific drugs from any and all manufacturers of that drug; each drug is separately bid; bids will be accepted on the generic equivalent as well as the therapeutic version of each drug; the manufacturer who submits the winning bid on each drug will become the only manufacturer of that drug that SRS will reimburse (when that manufacturer's brand of the drug is used by Medicaid/ MediKan recipients); only one manufacturer for each type of drug will be so designated and SRS will not reimburse for brands of the same drug manufactured by unsuccessful bidders; when a participating provider-pharmacist dispenses the designated drug to a Medicaid/MediKan recipient, that Medicaid/MediKan recipient must pay a flat co-payment fee to the pharmacist;

the provider-pharmacist then submits a claim to SRS; SRS reimburses the participating provider-pharmacist for the costs of the designated drug that the co-payment fee did not cover; SRS then takes all the claims it has received from participating provider-pharmacists and submits those claims and amounts to the bid winner for each drug; the winning drug manufacturer then gives a rebate to SRS for the difference between the amount SRS paid to the provider-pharmacist and the amount of the winning bid price.

For example: (1) the winning bid is accepted from a manufacturer at $1.00 per unit for drug Z; (2) drug Z is sold by the manufacturer to a participating provider-pharmacist for $2.50 per unit; (3) a Medicaid/MediKan recipient buys drug Z from that participating provider-pharmacist, who charges a retail price for the drug of $5.00 per unit; (4) the Medicaid/MediKan patient pays the required flat fee co-payment of .50 cents per unit; (5) the participating provider-pharmacist submits a claim for the unpaid cost of the drug, $4.50 or $2.00 (dependent upon whether SRS reimburses wholesale or retail costs); (6) SRS submits a claim to the winning manufacturer for the difference between the provider-pharmacist claim ($4.50 or $2.00) and the winning bid ($1.00), $3.50 or $1.00. The amount paid from the winning manufacturer to the state is characterized as a rebate. The rebate paid to SRS from the winning bid manufacturer will be paid to the state general fund.

SRS believes this bid program will result in cost containment for the state and has used this drug bid procedure for almost two years. Approximately 95% of all Kansas pharmacies participate in supplying drugs to Medicaid/MediKan recipients.

Certain unavailable information may have a significant impact upon the permissibility of the proposed bid program: details concerning geographic market; the relevant market share and market power; the intentions of the participating states or other entities; the exact nature of the interstate cooperation agreement; each participating state's enabling legislation; and the length of time the bid and the interstate agreement will be in effect. As we do not have specific information concerning these and other possible fact issues, this opinion is general in nature and is limited to a discussion of antitrust principles as they apply to the facts currently before us. It is hoped that the discussion contained herein will provide guidance and allow SRS to conduct the bid program procedure in accordance with and mindful of antitrust principles.

You state that the details and terms of a multi-state program have not been established. Because many states are interested in participating and because the successful bid winner's brand could become the only brand that states will reimburse Medicaid recipients for, the successful bid winner could significantly increase or assure itself of a large market for each drug. The geographic market, market share and relevant market for each successful bidder cannot be ascertained at this point. Nevertheless, it is obvious that should a significant number of states participate nonsuccessful bidders could potentially lose or be precluded from obtaining a significant amount of business. Nonsuccessful bidders would be able to sell their product to pharmacies wishing to stock their brands and pharmacists remain able to sell any brand of drug to the general public or to state and federal aid recipients, but any Medicaid recipient wishing to have the state pay drug costs will have to purchase the approved brand. Thus, pharmacists have a strong incentive to stock adequate quantities of that brand and Medicaid recipients are extremely likely to request that brand.

The general purpose of antitrust laws is the subject of much discussion between legal authority and economists. Broadly and generally stated, antitrust laws seek to promote, encourage and maintain competition and to prevent harmful monopolies. See generally City of Chanute, Kansas v. Williams Natural Gas Company, 678 F.Supp. 1517 (Kan. 1988); 54 Am.Jur.2d Monopolies § 1 (1971); 58 C.J.S. Monopolies § 15 (1948).

The Sherman Act, 15 U.S.C. §§ 1-7, forbids monopolizing trade in broad and general terms. Violation requires the possession of monopoly power in a relevant market and the knowing intentional acquisition of that power by two or more conspirators. *McKenzie v. Mercy Hospital of Independence, Kansas*, 854 F.2d 365, 367 (10th Cir. 1988). The Clayton Act, 15 U.S.C. §§ 12-27, prohibits specific anticompetitive behavior outside the broad scope of the Sherman Act. *See generally* 54 Am.Jur.2d *Monopolies* § 111 (1971). The Clayton Act seeks to promote competition through protection of viable, small and locally owned businesses. *Ford Motor Company v. United States*, 405 U.S. 562, 92 S.Ct. 1142, 31 L.Ed.2d 492 (1972). The Robinson-Patman Act was enacted to strengthen sections of the Clayton Act and seeks to protect small businesses unable to purchase in quantity. *See FTC v. Morton Salt*, 334 U.S. 37, 68 S.Ct. 822, 92 L.Ed. 1196 (1948). State antitrust laws vary in scope and application and each participating state must examine its own antitrust laws.

In order to determine whether a particular action violates antitrust laws it becomes necessary to characterize the questioned or challenged activity. Antitrust principles look at two types of anticompetitive relationships, horizontal and vertical. Horizontal restraints are arrangements between entities operating on the same level; manufacturers, suppliers or buyers. The proposed interstate drug bidding arrangement could be characterized as a horizontal arrangement between two entities operating on the same level, *i.e.* states as buyers or insurers. Practices that may result in a prohibited horizontal restraint include price fixing, boycotts of a product, manufacturer or customer, and mergers resulting in a monopoly. *See* Vakerics "Antitrust Basics", pp. 6-1 through 6-49 (1988). Vertical restraints are conditions or restrictions agreed to, imposed or directed at entities operating at different levels. Vertical relationships which may exist in the proposed drug bidding program include the relationship between the states and the drug manufacturers, the states and the provider-pharmacists, the states and the general public, and the states and the benefit recipients. Vertical restraints include dictating resale prices, *Arizona v. Maricopa County Medical Society*, 457 U.S. 332, 102 S.Ct. 2466, 73 L.Ed.2d 48 (1982), or non-price restraints such as territorial or customer restrictions, price discrimination, exclusive dealing or requirement contracts, and tie-ins. Antitrust restraints that may be implicated by the proposed bid program include price fixing, boycott, price discrimination, and requirement contract considerations.

Price fixing restraints are traditionally considered *per se* illegal, while non-price restraints are more often subject to the rule of reason. Courts currently evidence a reluctance to impose a *per se* rule unless there is clear evidence of intent to monopolize or otherwise hinder helpful competition. Rather, courts now frequently use a rule of reason analysis to determine antitrust violations. Under the "rule of reason" the legality of restraints on trade is determined by weighing all the factors in a case, such as the history of the restraint, the evil believed to exist, the reason for adopting the particular remedy and the purpose or ends thought to be attained. Blacks Law Dictionary 1196 (5th ed. 1979).

Generally, price fixing is any combination formed for the purpose and effect of raising, depressing, pegging, or stabilizing the price of a commodity. *United States v. Socony Vacuum Oil Company*, 310 U.S. 150, 223, 60 S.Ct. 811, 84 L.Ed. 1129 (1940). Sharing information on prices may also result in improper price fixing. *See United States v. Container Corporation of America*, 393 U.S. 333, 89 S.Ct. 510, 21 L.Ed.2d 526 (1969). However, where third parties are not affected by the price fixing scheme, a rule of reason will usually be applied. *Medical Arts Pharmacy v. Blue Cross and Blue Shield*, 675 F.2d 502 (2d Cir. 1982). *See generally* Hjelmfelt, "Antitrust and Regulated Industries", pp. 42-45 (1985).

The proposed bid program does not appear to be a vertical or horizontal price fixing scheme. The states are a large buyer or buyers seeking the lowest price on a commodity. If the states were considered competitors there could be a possible horizontal price fixing charge against them. However, the proposed drug bid program does not dictate and will not automatically affect the price charged to and paid by participating provider-pharmacists to the drug manufacturer. Moreover, the resale price to the general public or benefit recipients is not dictated by the drug bidding program. The bid reflects the price at which each manufacturer independently agrees to ultimately provide the drugs to the state or states. The states ask that each manufacturer fix its own individual price, and the states remain free to either accept or reject each bid. Thus, the price is fixed by the manufacturer not by the states, and it is therefore unlikely that a price fixing claim would succeed.

Another possible antitrust principle that may be involved concerns boycotts. A boycott is "a method of pressuring a party . . . by withholding or enlisting others to withhold patronage or services." St. Paul Fire and Marine Insurance Company v. Barry, 438 U.S. 531, 541, 98 S.Ct. 2923, 57 L.Ed.2d 932 (1978). A boycott may be illegal if it impermissibly increases market strength through concerted efforts.

The Fifth Circuit held that a per se rule would be applied to boycotts only when there was evidence of an anticompetitive motive, a commercial purpose rather an industry self-regulation, and coercive economic pressure. St. Bernard General Hospital v. Hospital Service Association, 712 F.2d 978 (5th Cir. 1983). When there is no evidence of exclusionary anticompetitive purpose, intent or conduct, a rule of reason generally applies. American Medical Association v. United States, 130 F.2d 233 (D.C. Cir. 1942), affd. 317 U.S. 519, 63 S.Ct. 326, 89 L.Ed. 434 (1943).

In the proposed drug bid program there is no obvious evidence that the states or the provider-pharmacists are getting together and refusing to deal with certain drug manufacturers for an anticompetitive purpose. The articulated reason for encouraging use of the successful bidder's brand by the states is to keep costs paid for these drugs at a minimum. The intent to contain costs is not a refusal to deal but rather an intent to obtain the most competitive price and thus to promote and encourage competition among suppliers.

Using the rule of reason analysis, cost containment represents a valid competitive purpose. Reasonable contract terms and free and open access to the bidding process will lessen the possibility of a successful boycott claim against the states. However, the fact that only one manufacturer will be approved for each drug, even if more than one drug manufacturer submits the same low bid, undermines this cost containment argument and purpose. Rather, the purpose of accepting only one manufacturer appears to be either administrative ease or an effort to increase the bargaining power of the states. We strongly suggest that price containment purposes remain the rationale and primary focus of the drug bidding program. Each and every manufacturer of a required drug should be given an equal opportunity and be encouraged to compete for this business. No intent to exercise exclusionary anticompetitive pressure should be evidenced or contemplated by participating states. If the states are satisfied that the bid price of more than one brand is the lowest price they can expect or get, it may be advisable to award the business to more than one manufacturer.

The proposed drug bid program also resembles a requirement contract, which is defined as "[a contract in which] one agrees to buy, for sufficient consideration, all the merchandise of a designated type which the buyer may require for use . . . one in which a party agrees to supply a specific good which another party may need during a certain period for an agreed price." Blacks Law Dictionary 1172 (5th ed. 1979). In the proposed bid program, the state agrees to ultimately pay the price of any drug used by a benefit recipient if that recipient uses the brand of a successful bidder. Thus, the insurer-state agrees to purchase all drugs of a particular type that it requires from one manufacturer. Requirement contracts are examples of non-price vertical restraints. The risk of antitrust problems increase in relation to the relative market power created by a requirements contract. Vakerics, "Antitrust Principles" § 7.1 (1988).

A requirement contract may violate antitrust law if an arrangement substantially lessens interbrand competition and competitors are seriously hindered or foreclosed from an available market for a significant period of time. See Tampa Electric Company v. Nashville Coal Company, 365 U.S. 320, 81 S.Ct. 623, 5 L.Ed.2d 580 (1961); Standard Oil Company of California v. United States, 337 U.S. 293, 69 S.Ct. 1051, 93 L.Ed. 1371 (1949). Several federal courts have examined the concept of exclusive dealing or requirement contracts in the health care field. These cases evidence a willingness to permit these arrangements if competition is not substantially lessened or a relevant market monopolized. See DosSantos v. Columbus-Cuneo-Cabrini Medical Center, 684 F.2d 1346 (7th Cir. 1982); White and White, Inc. v. American Hospital Supply Corp., 540 F.Supp. 951 (Mich. 1982), rev'd on other grnds, 723 F.2d 495 (6th Cir. 1983).

In Medical Arts Pharmacy of Stanford, Inc. v. Blue Cross & Blue Shield of Conn., Inc., 518 F.Supp. 1100 (D. Conn. 1981), aff'd per curiam, 675 F.2d 502 (2d Cir. 1982), the district court found that the defendant insurer was the purchaser even though the insureds actually used and obtained the drug. The second circuit court seems to imply that if market share is large enough there may be sufficient monopsony power exercised by one large buyer to sustain a competitive seller's claim that a pharmaceutical purchasing agreement obtained without collusion could be anticompetitive and a violation of the Sherman Act. See also Sutliff, Inc. v. Donovan Cos., 727 F.2d 648, 655 (7th Cir. 1984); Pan-Islamic Trade Corp. v. Exxon Corp., 632 F.2d 539, 547 (5th Cir. 1980); Quality Auto Body, Inc. v. Allstate Ins. Co., 660 F.2d 1195 (7th Cir. 1981) cert. den. 455 U.S. 1020 (1982). (Monopsony; "a condition of the market in which there is but one buyer for a particular commodity." Blacks Law Dictionary 908 (5th ed. 1979).)

Most joint buying arrangements have potential efficiencies which remove them from per se violation of antitrust laws. Under the rule of reason, agreements or combinations may be prohibited if they prejudice the public interest by unduly restricting competition or obstructing the course of trade. Reazin v. Blue Cross and Blue Shield of Kansas, Inc., 635 F.Supp. 1287 (Kan. 1986). In a 1987 paper presented to the National Health Lawyers Association Conference on Antitrust Law in the Health Care Field, Michael L. Denger stated that the Federal Trade Commission considers government insurance programs to be purchasers of health care services, thus making such programs part of a relevant market. However, Mr. Denger noted that membership in a prepaid prescription drug organization making up less than 30 percent of the retail pharmaceutical sales in a geographic market will probably not be challenged by the Justice Department. Other authorities believe obtaining more than 17 to 20 percent of a relevant or geographic market will result in an antitrust law violation. It therefore becomes necessary to determine the geographic market for each drug and of each manufacturer in the bid program and what percentage of the relevant market will be given to the winning manufacturer as a result of the proposed bid program. This requires detailed factual information concerning the amount of a particular type of drug sold nationally, and in each participating state or area, and what percentage of those sales could, pursuant to this bid program, be given exclusively to the winning manufacturer. When the market share does not confer market power, anticompetitive claims become less plausible. However, antitrust laws may prohibit the proposed bid program if it allows one manufacturer to obtain an unusually large share of a relevant market, thus essentially reducing or precluding all helpful competition. The length of time that the agreement will allow the winning manufacturer to obtain this market share will also be relevant.

Unless a substantial share of a relevant market is foreclosed for a significant period of time, or unless there is an anticompetitive purpose or intent, an exclusive dealing or requirements contract will generally not present antitrust problems under a rule of reason analysis. Vakerics at § 7.09. We therefore suggest that any agreement entered into between the states or between an individual state and a pharmaceutical manufacturer be for a limited time period and initially allow every manufacturer equal access to this particular market. Once the proposed bid program and the degree of state participation is determined, an analysis of the pertinent market data can be made. It is our opinion that, under the rule of reason, unless there is an anticompetitive intent or a large percentage of the entire market for each particular drug will be foreclosed to other manufacturers for a significant period of time, the proposed drug bid program does not represent impermissible large scale buying or a prohibited requirement contract.

15 U.S.C. § 13(a) discusses price discrimination. Most recent price discrimination cases do not involve governmental prosecution, but rather, are brought by parties allegedly harmed by the behavior. Illegal price discrimination may be alleged by nonparticipating states, pharmaceutical companies who lose business, or members of the public or provider-pharmacists who do not receive the same price. Without specific information we cannot discuss the merits or standing of such challenges. Generally, any unwarranted price favoritism shown by suppliers to larger purchases not based on permissible justifications or defenses may be a violation of antitrust laws. See Gianelli Distributing Company v. Beck and Company, 172 Cal.App.3rd 120, 219 Cal. Rptr. 230 (1985); Jefferson County Pharmaceutical Association Inc. v. Abbbott Laboratories, 460 U.S. 150, 103 S.Ct. 1011, 74 L.Ed.2d 882 (1983); Portland Retail Drug Association v. Kaiser Foundation Health Plan, 662 F.2d 641 (9th Cir. 1981).

The price paid by the pharmacist and the patient-purchaser for each particular drug is not necessarily altered by the drug bid program. Rather, the drug bid program establishes the ultimate price that the state insurer will pay for the drug. The same drug (with the same shipping, manufacturing and other associated costs) will ultimately be made available to the state at a potentially different and lower price than the price paid by others. The provider-pharmacist will not necessarily be charged less for the drugs used by Medicaid/MediKan recipients. Ultimately, however, others may pay more for the same drug.

15 U.S.C. § 13b permits rebates from a cooperative association to its members, producers, or consumers, but rebates may not be used to violate price discrimination laws. See Bargain Car Wash, Inc. v. Standard Oil Company, 466 F.2d 1163 (7th Cir. 1972). The fact that the states are paying a potentially lower price for the same drugs may not represent price discrimination if a valid defense can be claimed. The defendant (often the supplier) in an antitrust case can rebut a claim of illegal price discrimination by showing that there are lower costs in serving this particular purchaser, changing conditions allow a change in price, or competition is met and justifies the lower price. See Hansen, "Robinson-Patman Law", LI Fordham L. Rev. 113 (1983).

Prices set or obtained by governmental entities may not represent price discrimination if the activity is of a governmental nature. Generally, the Robinson-Patman Act does not apply to sales made to the government. See Gaslight Company of Columbus v. Georgia Power Company, 313 F.Supp. 860, 440 F.2d 1135, cert. den., 404 U.S. 1062, 92 S.Ct. 732, 30 L.Ed.2d 750 reh. den., 405 U.S. 969, 92 S.Ct. 1162, 31 L.Ed.2d 244 (1970). However, governmental immunity is not extended to every act or every price set by a governmental entity. See Jefferson County Pharmaceutical Association, Inc. v. Abbott Laboratories, 460 U.S. 150, 103 S.Ct. 1011, 74 L.Ed.2d 882 (1983). Immunity from antitrust laws exists for a governmental entity if (1) the challenged restraint is one clearly articulated and affirmatively expressed by state policy and (2) the policy itself is actively supervised by the state. See Russell v. City of Kansas City, Kansas, 690 F.Supp. 947 (Kan. 1988).

Using the analysis articulated in *Russell*, SRS and other state agencies may be able to make a legitimate argument that involvement in drug bidding programs is immune from antitrust laws. Most social welfare agencies are given authority to administer the state's medical programs and thus the argument can be made that the legislature's authorization of that administration either contemplated the resulting anticompetitive effects or such activities were a reasonably foreseeable consequence of the authorization. However, those challenging this activity may argue that the legislature allows SRS (and other equivalent agencies) to provide medical care, not to set prices in violation of antitrust laws. *Jefferson County*, 460 U.S. 150, 103 S.Ct. 1011, 74 L.Ed.2d 882 (1983), involved the sale of pharmaceutical products to state and local government hospitals in competition with private pharmacies. The Court, in a five to four decision, held that these actions were not exempt from the Robinson-Patman Act. However, the opinion noted that "we are not concerned with . . . state purchases for use in traditional governmental functions . . . [nevertheless] we conclude that the exemption does not apply where a state has chosen to compete in the private retail market." *Id.* at 153-154. In footnote seven the court acknowledged that it was not addressing whether sales by the state to indigents were in competition with private enterprises. Thus, this remains an unresolved issue.

Kansas legislators have given SRS broad authority in the area of medical care benefits for qualified persons. This delegation has allowed SRS much regulatory and discretionary authority concerning implementation of the benefits program. If SRS authorities exercise this delegated authority by participating in the drug bid program and the legislature does not act to limit this authority, it is our opinion that, even if an antitrust law would otherwise be violated, governmental immunity may allow SRS to take part in this program. Agencies from other states who wish to participate in the proposed drug bid program must individually examine whether their state's policies and enabling acts authorize participating in such a program and whether the state actively supervises its implementation.

In conclusion, although the proposed bid program raises serious antitrust questions, we believe it does not represent a *per se* violation of antitrust laws. Under a rule of reason analysis, the proposed drug bid program may survive an antitrust challenge. The drug bid program should be conducted so as to provide that (1) each manufacturer is given an equal and meaningful opportunity to compete for this business, with no voice in determining which manufacturer is selected, (2) the participant states should not be competing purchasers who conspire to fix a buying price, (3) objective bidding criteria should be maintained, (4) each participant pharmacist, benefit recipient and purchaser should remain free to select any and all pharmaceutical providers with which they wish to contract, (5) the winning manufacturer should not be allowed to possess a market power that unreasonably excludes or eliminates all competition, and (6) the terms of the agreement should be for a reasonable and limited time period. If, under the rule of reason analysis, a potential antitrust violation remains a possibility, governmental immunity may nevertheless allow the activity if: (1) each participating state agency has authority to enter into such an arrangement; (2) the state actively supervises the program; and (3) the anticompetitive results are expected or foreseeable. Specific legislative enactment allowing each aspect of the program could effectively negate most claims that the participating states violated antitrust laws.

Very truly yours,

Robert T. Stephan

ROBERT T. STEPHAN
ATTORNEY GENERAL OF KANSAS

Theresa Marcel Nuckolls

Theresa Marcel Nuckolls
Assistant Attorney General

RTS:JLM:TMN:bas

1988-1989 BID CONTRACT DRUGS

Drug Class (& Usage)	Representative Brand Name	Generic Name	Brand Average Wholesale Price	Representative Generic Average Wholesale Price	Bid/ Contract Net Price
Antibiotic for infections	Keflex	Cephalexin 250 mg	$0.7646 cap	$0.4785	$0.2095
Antibiotic	Keflex	Cephalexin 500 mg	1.5026 cap	0.9209	0.4075
Diuretic for blood pressure	Dyazide	Triamterene/ HCTZ 50/25	0.5657 cap	0.3863	0.2688
Diuretic	Maxzide	Triamterene/ HCTZ 75/50	0.4095 tab	0.2790	0.2000
Diuretic	Zaroloxyn	Metolozone 5 mg	0.2321 tab	No generic	0.1198 tab
Antacid for ulcers, etc.	Amphojel	Aluminum Hydroxide	0.0099 ml	0.0082 ml	0.0051 ml
Potassium Supplement for use with some diuretics	Micro-K	Potassium Chloride Sustained Release/10mEq	0.0905 cap/tab	0.0713 cap/tab	0.0425 tab
Bronchodilator for breathing problems	Theolair	Theophylline 80mg/15ml	0.0265 ml	0.0068 ml	0.0040 ml

A commonly prescribed representative brand name is shown followed by the generic name of the drug entity, with the dosage form and dose. The three cost columns list the then current brand cost and a representative generic company's cost, both at Average Wholesale Price (AWP) and the final net cost to the state under the actual contract.

Notes: The cost figures are by dosage unit (tablet or capsule) for the oral solids, and by milliliter volume (ml) for the liquids. Some brand and generic prices have changed since these contracts were signed, but the bid price remained constant. There are no generics of metolozone, but there are two brand names of the product marketed by different companies.

EES:csl
06/26/89

Appendix 6

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

P84-18
FOR IMMEDIATE RELEASE
October 24, 1984

Food and Drug Administration
Susan Cruzan (301) 443-3285
Home (301) 972-4222

Secretary of Health and Human Services Margaret M. Heckler today announced Food and Drug Administration approval of a drug which effectively treats a fatal form of pneumonia that often strikes AIDS patients and others with disorders of the immune system.

About 60 percent of AIDS patients develop this form of pneumonia (called Pneumocystis carinii pneumonia for the protozoa or microscopic organism that causes the disease.) If untreated, that form of pneumonia is almost always fatal.

The drug, pentamidine, is an antiprotozoal agent that studies suggest inhibits synthesis of RNA and DNA by protozoa.

Its use can cure one of the chief killers of AIDS patients. While the drug is already available from a foreign manufacturer and is distributed by the Centers for Disease Control, today's approval will ensure a continuing U.S. supply.

LyphoMed Inc. of Melrose Park, Ill., will begin marketing the drug within the next few weeks under the brand name Pentam 300. Until that time, the Centers for Disease Control in Atlanta will continue to distribute the drug as an investigational drug. The drug is administered either intramuscularly or intravenously, usually in a hospital.

FDA Commissioner Frank E. Young, M.D., said, "Scientists at CDC, FDA and the company have worked closely to ensure that this lifesaving drug will continue to be readily available to patients in the United States."

-MORE-

Until 1981 when AIDS was recognized as a distinct disease condition, this pneumonia occurred only in immunocompromised patients, cancer patients and premature infants. Then, an increased incidence of P.carinii pneumonia and increased requests for pentamidine led CDC scientists to recognize that a new disease syndrome, subsequently identified as AIDS, was occurring in homosexuals, hemophiliacs, Haitians and users of illicit intravenous drugs.

At that time, pentamidine was being made available on request by the Centers for Disease Control which obtained it from a pharmaceutical company in England. But the increasing demand for the drug and uncertain availability of the overseas supply led CDC and FDA to recruit a manufacturer and distributor to make the drug commercially available in the United States.

Pentamidine is a potent drug with known toxicity. It has been used as an alternative treatment for patients who have developed allergic reactions or who do not respond to treatment with sulfamethoxazole-trimethoprim, the only other available drug for P.carinii. Reported adverse reactions to pentamidine include severe low blood pressure, decrease in blood sugar, irregular heartbeats and kidney impairment.

Pentam 300 has been designated an orphan drug under the Orphan Drug Act of 1983 which offers special incentives to manufacturers to produce drugs with little commercial value.

#####

National Organization for Rare Disorders Inc.
NORD • P.O. Box 8923 • New Fairfield, CT 06812 • 203/746-6518

...out of the darkness, into the light...
NORD

[illegible]

December 1, 1987

Dr. John N. Kapoor
President & CEO
Lyphomed LM, Inc.
10401 W. Touhy Ave.
Rosemont, IL 60018

Dear Dr. Kapoor:

During previous years we have communicated on a regular basis with Sandy Hagenbrock and Kathy Norvalitis of Lyphomed. We believe that Lymphomed has been an outstanding model for the pharmaceutical industry as a developer of orphan drugs.

Each year the National Organization for Rare Disorders (NORD) presents awards to people and corporations at our annual banquet in Washington, DC. We are pleased to inform you that Lymphoned LM, Inc., will be the recipient of one of our 1988 corporate awards along with Merck and Sandoz.

NORD's Annual Tribute Banquet will be held on April 18, 1988 from 6 p.m. to 10 p.m. at the Hyatt Regency Hotel in Crystal City (near National Airport just outside of Washington, DC). Last year over 300 people attended and we expect even more at the 1988 event. Attendees are primarily composed of pharmaceutical manufacturers (both PMA and generic corporations), scientists, government leaders, NIH and FDA personnel, reporters and consumers.

Enclosed you will find a copy of last year's Banquet Journal. We are always pleased to know that Lyphomed has been a consistent supporter of NORD through journal ads in previous years.

Besides three corporate awards at the Banquet, we will also be honoring Senator Lowell Weicker, Mrs. Alice Fordyce of the Lasker Foundation and Dr. Frank Young, Commissioner of the FDA.

We wish to honor Lyphomed for its consistent and agressive pursuit of new orphan drugs and, particularly, because you were willing to adopt pentamidine at a time when no one was able to predict the scope of the AIDS epidemic. NORD was involved with initial negotiations for this drug which, at the time, was unattractive to numerous pharmaceutical companies because only a few hundred people had been identified with AIDS. We were grateful for Lyphomed's willingness to adopt pentamidne when no other company stepped forward. Thus the Tribute Banquet offers an opportunity to say "thank you" publicly.

NORD RESEARCH ADVISORY COUNCIL

Chairman
Eugene Gardner
Vice Chairman
Milton [illegible]
Secretary
Richard L. Goldberg

Treasurer
William Haddad
Mary Ellen Brademas, M.D.
Edward N. Brandt, Jr., M.D.
Craig Burrell, M.D.
Harold Burson

Michael DeBakey, M.D.
Marion Finkel, M.D.
Alice Fordyce
George Goldstein, M.D.
Senator Nancy L. Kassebaum
Mathilde Krim, Ph.D

Ronald Kurtzman, Ph D
Wayne Pines
Harvey Sadow, M D
Jacob M. Schain
Rep. Henry Waxman

Dedicated to Helping People with Orphan Diseases

7

Please let us know who will accept the award on behalf of Lyphomed LM, Inc., at our 1988 Tribute Banquet. We look forward to your reply and acceptance of this honor. A response by December 18th is appreciated.

Very truly yours,

Abbey Meyers

Abbey S. Meyers
Executive Director

ASM:sb

cc: Dr. Mahendra Shah
Jess Thoene, M.D., President
Shirley Friedland, Event Coordinator
Gene Gardner, Research Advisory Council

. . . out of the darkness • into the light . . .

THIRD ANNUAL TRIBUTE BANQUET

April 18, 1988

NORD

. . . out of the darkness, into the light . . .

NORD • P. O. Box 8923 • New Fairfield, CT 06812 • (203) 746-6518

LYPHOMED INC.

Lyphomed was a small generic manufacturer of intravenous medications when it indicated an interest in Orphan Drug development. During 1982, a small meeting was convened in Washington where a representative of the Centers for Disease Control (CDC) mentioned that a new disease had been identified; no one knew the cause, but it was inevitably fatal – usually from P. Carinii pneumonia. The disease was later identified as AIDS.

There was only one medication - Pentamidine - for P. Carinii pneumonia which was no longer manufactured by a British corporation for treatment of Rhodesian Sleeping Sickness. The world's remaining supply of the drug had been destroyed by water contamination while in storage. Therefore, Lyphomed agreed to step in during this emergency situation to manufacture the drug. At that time, CDC estimated that only between 300 and 600 cases of AIDS had been identified in the U. S. Within months, Pentamidine was made available to Americans with AIDS due to Lyphomed's commitment. Subsequently, the company has adopted several other orphan drugs and stands ready to develop still more life-saving therapies. For this commitment, NORD presents its 1988 Corporate Leadership Award to Lyphomed, Inc., with gratitude.

JUL 20 1988

NOTE: THIS GUIDANCE IS BEING ISSUED ON A PILOT BASIS AND IS SUBJECT TO CHANGE AND/OR CANCELLATION. IF THE PILOT PROVES SUCCESSFUL, WITH NO SIGNIFICANT PROBLEMS, CHAPTER 9-71 OF THE REGULATORY PROCEDURES MANUAL MAY BE APPROPRIATELY REVISED.

SUBJ: Pilot Guidance for Release of Mail Importations

Because of the desire to acquire articles for treatment of serious and life-threatening conditions like AIDS and cancer, individuals have been purchasing unapproved products from foreign sources. Some of these products are sold over-the-counter in the country of origin while others are available from clinics where the purchaser was treated. Such products are often shipped to the purchaser by mail.

Even though such products are subject to refusal, we may use our discretion to examine the background, risk, and purpose of these products before making a final decision. To assure that the districts are operating in a uniform manner, the following guidance is provided for dealing with personal use shipments.

1. Except as modified by these instructions, established guidance found in RPM-9-71, exhibits X9-71-1 and X9-71-2 should be followed.
2. A product entered for personal use, which meets the criteria in item 4 below, may proceed without sampling or detention.
3. Products that are not identified, or are not accompanied by documentation of intended use, should be detained. Other reasons for detention may include: size of the shipment (amount inconsistent with personal use), fraudulent promotion or misrepresentation, or an unreasonable health risk due to either toxicity or possible contamination. In such cases, the approppriate center should be contacted for guidance concerning release of the product.
4. Following detention, shipments may be released to an individual if the following criteria can be satisfied and there is no safety risk or evidence of fraud:
    - o the product was purchased for personal use
    - o the product is not for commercial distribution and the amount of product is not excessive (i.e., 3 months supply of a drug)
    - o the intended use of the product is appropriately identified
    - o the patient seeking to import the product affirms in writing that it is for the patient's own use and provides the name and address of the doctor licensed in the U.S. responsible for his or her treatment with the product
5. If the district should encounter a situation suggesting promotional and/or commercial activity that falls within our health fraud guideline, the district should recommend that an Import Alert be issued for the automatic detention of the product and identification of the promoter involved.
6. The model letter currently in Exhibit X9-71-2 should be revised according to the attached during this pilot.
7. The article may then be RELEASED WITH COMMENT upon receipt of the letter as follows:

> "The drug you have obtained for your personal use appears to be unapproved in the U.S. We understand you will use this limited quantity under medical supervision; however, future personal shipments may be refused entry if we learn, among other things, the drug presents an unreasonable risk or it has been commercially promoted to U.S. citizens."

The above guidance should be used as part of the current outstanding instructions for dealing with mail packages as found in Chapter 9-71 of the RPM.

Import Operations Branch
5600 Fishers Lane
Rockville, MD 20857
(301) 443-6553

MODEL LETTER FOR USE IN DRUG MAIL EXHIBIT X9-71-2

(LETTERHEAD)

A mail shipment of a drug from a foreign country addressed to you is being detained at the post office. All products of this kind must meet the requirements of the Federal Food, Drug, and Cosmetic Act, which is designed to protect you from unsafe or misrepresented foods, drugs, cosmetics and devices. Examination indicates that the product does not comply with the law.

Please read the enclosed Notice of Detention and Hearing carefully, since it explains why the product is believed to be in violation. The Notice does not in any manner accuse you of violating any law.

If the drug is not approved for distribution in the U.S., it may be released for your personal use provided you furnish the following:

> A letter providing adequate documentation that the product is for the patient's own use and the name and address of the doctor licensed in the United States responsible for his or her treatment with the product.

Send your statement to this office, and we will promptly review your submission and consider release of the product.

If you have good reason to believe the product does comply with the law and wish to discuss it with us, you may come personally to this office or write to us within the time limit shown on the Notice.

If you do not wish to claim this shipment, you may disregard the Notice and the shipment will be returned to sender without cost to you.

Sincerely yours,

Enclosure

Hand Delivered 076/89

"CONFIDENTIAL EXCEPT
AS TO PRODUCT PRICING"

FISONS
Fisons Corporation
Two Preston Court
Bedford, Massachusetts 01730
Telephone (617) 275-1000
Telex 200066 FISN UR
Cables Fisons Bedfordmass

March 9, 1989

Ellen C. Cooper, M.D. (HFD 530)
Director
Division of Anti-Viral Drug Products
Office of Drug Review II
Center for Drug Evaluation
and Research
Food and Drug Administration
Room 15B-45
5600 Fishers Lane
Rockville, MD 20857

Re: Fisons Corporation
IND 30,361
NDA 19-874
Pneumopent™ (pentamidine isethionate for inhalation)

Dear Dr. Cooper:

[Proprietary information excised]

"CONFIDENTIAL EXCEPT
AS TO PRODUCT PRICING"

A Comparison of the Two Drug Regimens

The drug regimens used by Fisons and by Lyphomed cannot readily be compared. Each uses a unique nebulizing device that is an essential element of the dosage delivery. The Fisons device is more efficient in its delivery of API to the lung, and Fisons has demonstrated the effectiveness of a dosage of 120 mg API per month (delivered in amounts of 60 mg API every other week), as contrasted with the Lyphomed dosage of 300 mg API per month. The Fisons device is portable and thus can be used in the home, whereas the Lyphomed device needs a supply of compressed air and can be used only at a clinic or hospital or with a portable compressor. Lyphomed is currently selling a dosage of 300 mg API at the cost of $99.50 per month under its treatment IND. Fisons is prepared to commit that it will charge no more than $50.00 per month for its dosage regimen, under either a treatment IND or an approved NDA. Thus, there are major differences between these two drugs and their dosage regimens.

[Proprietary information excised]

Conclusion

Fisons believes that, using the same rigorous scientific criteria that FDA customarily demands for double-blind, placebo-controlled trials on new drugs, the safety and effectiveness of its API dosage regimen has now been established with a remarkably high degree of statistical confidence. Accordingly, we believe that FDA should grant prompt approval of a treatment IND, and subsequently of an NDA, for our Pneumopent™ dosage regimen.

"CONFIDENTIAL EXCEPT
AS TO PRODUCT PRICING"

Because the status of API has been of widespread interest within FDA, NIAID, and indeed the scientific community and the public at large, we are providing courtesy copies of this letter to appropriate officials both in FDA and at NIAID.

Very truly yours,

Susan R Raymond

Susan R. Raymond
Senior Regulatory Affairs
Associate

SRR:1311L

cc: Food and Drug Administration:
James M. Bilstad, M.D. (HFD-500)
D. Bruce Burlington, M.D. (HFD-501)
Joseph A. Levitt, Esquire (HF-9)
Mr. Gerald F. Meyer (HFD-2)
Paul D. Parkman, M.D. (HFB-1)
Carl C. Peck, M.D. (HFN-1)
Thomas Scarlett, Esquire (GCF-1)
Robert Temple, M.D. (HFD-100)
Carol B. Trapnell, M.D. (HFD-530)
Frank E. Young, M.D., Ph.D. (HF-1)
Document Control Room 15B-45

National Institute of Allergy and Infectious Diseases:
Anthony S. Fauci, M.D.
Daniel F. Hoth, M.D.
Henry A. Masur, M.D.
Maureen W. Myers, Ph.D.

FISONS
Pharmaceuticals

Fisons Corporation
Jefferson Road
Post Office Box 1710
Rochester, New York 14603
Telephone (716) 475-9000
Telex 4441031 AREX RUI
FAX (716) 475-1016

"CONFIDENTIAL EXCEPT
AS TO PRODUCT PRICING"

April 18, 1989

Henry Masur, M.D.
Chairman,
Public Health Service Task Force on
Anti-Pneumocystis Prophylaxis
Clinical Center, 10D48
National Institutes of Health
Bethesda, MD 20892

RE: Aerosol Pentamidine in Prophylaxis of PCP

Dear Dr. Masur:

[Proprietary information excised]

It has occurred to me that a task force paper in this area may well address the aspects of health benefits derived from successful prophylaxis particularly where, as with our regimen, the nebulization device allows for fairly easy home health care. If your paper in fact intends to address the aspects of cost savings through this intervention, I am pleased to be able to confirm to you that Fisons Corporation has decided that its price for a unit of Pneumopent will be twenty dollars. This twenty dollars per vial cost would translate into a monthly drug maintenance cost of forty dollars (for a total of 120 mg pentamidine). You and your colleagues would be better situated to estimate the benefits derived through avoidance of costly hospitalizations with PCP

"CONFIDENTIAL EXCEPT
AS TO PRODUCT PRICING"

Henry Masur, M.D.
April 18, 1989
Page 2 of 2

We trust that you will find this information helpful and will contact us if we can be of assistance.

Sincerely yours,

James M. Parker

James M. Parker, J.D., Ph.D.
Senior Vice President
Research and Development (U.S.A.)

JMP/tp

cc: Mr. B. W. Simpson, Sr. Vice President, Sales & Marketing
Mr. S. C. Attwood, President, Fisons Corporation
Dr. Ellen C. Cooper (HFD 530) Division of Anti-Viral Drug Products
Food and Drug Administration

CONFIDENTIAL

"CONFIDENTIAL EXCEPT
AS TO PRODUCT PRICING"

FISONS
Pharmaceuticals

Fisons Corporation
Jefferson Road
Post Office Box 1710
Rochester, New York 14603
Telephone (716) 475-9000
Telex 4441031 AREX RUI
FAX (716) 475-1016

May 5, 1989

Frank E. Young, M.D. Ph.D.
Commissioner of Food and Drugs
Department of Health and Human Services
Food and Drug Administrations
Rockville, MD 20857

Reference: Aerosol Pentamidine in PCP Prophylaxis

Dear Dr. Young:

[Proprietary information excised]

"CONFIDENTIAL EXCEPT AS TO PRODUCT PRICING"

Frustration aside, we believe that the FDA is now in a unique position of being able to approve the Fisons NDA and thereby effect a tremendous economic savings while giving patients protection from PCP with a lower dose of drug than that proposed by the competition. The Fisons drug maintainance cost on a monthly basis is $40 as compared with $100 for Lyphomed. Thus, if the FDA approves our application, public interest is well served. We need to meet with you, therefore, to confirm that there is no technical or policy blockade preventing marketing approval of Pneumopent™.

Would you please advise if it would be possible to meet on May 11, 12, or 15. In addition to myself, Dr. Parker would be in attendance. Mr. Fothergill, Chairman of Fisons Corporation, and a Director of Fisons plc may wish to attend this meeting or have a subsequent opportunity to meet with you, and a senior representative of MSKCC may also wish to attend.

Sincerely yours,

S.C. Attwood

Stephen C. Attwood
President
Fisons Corporation

PCMAIL -ECHO
MAIL IMPORT-ALERT 'IMPORT ALERT #66-50'

DATE: OCTOBER 4, 1989

FROM: DIRECTOR, DIVISION OF FIELD INVESTIGATIONS (HFC-130)

SUBJ: IMPORT ALERT #66-50 "AUTOMATIC DETENTION OF PENTAMIDINE ISETHIONATE"

TO : IMPORT PROGRAM MANAGERS

INFO: ALL MAJOR FIELD OFFICES
RESIDENT POSTS

GCP-1 (A. LEVINE)
HFB-100 (T. BOZZO)
HFC-6 (CONTAMINANTS POLICY STAFF)
HFC-41 (S. LARSON)
HFC-50 (INTERGOV & IND AFF STF)
HFC-101 (A. SHROFF)
HFC-140 (DV. OF FIELD SCIENCE)
HFC-150 (DV. OF FED-STATE REL)
HFC-160 (R. SWANSON)
HFC-200 (OFFICE OF ENFORCEMENT)
HFC-210 (C. EVERLINE)
HFC-230 (E. BRISSON)
HFD-300 (D. MICHELS)
HFD-301 (S. YOUNG)
HFF-25 (E. STEELE)
HFF-26 (FIELD PROGRAMS BRANCH)
HFF-300 (OFF. COMPLIANCE)
HFF-310 (OFF. REG. GUIDANCE)
HFF-314 (IMPORT FOODS SECTION)
HFI-20 (PRESS OFFICE)
HFI-21 (PRESS OFFICE)
HFV-230 (EDWARD BALLITCH)
HFW-10 (OFF. LEG. AFFAIRS)
HFY-50 (J. HARTY)
HFZ-300 (W. GUNDAKER)
HPB-CANADA (B. WILLIAMS)

TYPE OF ALERT: AUTOMATIC DETENTION

PRODUCT : Pentamidine Isethionate

PRODUCT CODE : 66 [ ][ ][ ][ ][ ]

PROBLEM : New drug without an approved New Drug Application (NDA) (DRND)

PAC : 56008H

COUNTRY : ALL

MANUFACTURER/
SHIPPER : ALL

CHARGE : "The article is subject to refusal of admission pursuant to Section 801(a)(3) in that it appears to be a new drug within the meaning of Section 201(p) without an approved new drug application [Unapproved New Drug, Section 505(a)]."

Section 801(a)(3) in that it appears to be a new drug within the meaning of Section 201(p) without an approved new drug application [Unapproved New Drug, Section 505(a)]."

RECOMMENDING OFFICE : Dallas District-HFR-SW140

REASON FOR ALERT : We have information that AIDS activist's groups have been importing and distributing unapproved Pentamidine Isethionate to AIDS patients in various cities. Press articles report the drug is being imported from England, Canada, and France. Because foreign products are not approved, FDA cannot independently assure the public of the composition, and purity of the drug being imported. (See Talk Paper #T-89, dated 10/4/89)

Pentamidine is used in the treatment and prevention of Pneumocystis Carinii Pneumonia, which is often associated with AIDS. The only FDA approval to date for this product is held by Lyphomed, Inc., Rosemont, IL. Also, Fisons is the only current holder of an IND (IND #30,361).

INSTRUCTIONS : Automatically detain all dosage forms and shipments, commercial and personal, of Pentamidine to determine if they are covered by a current approved NDA or IND. FDA has concluded that personal shipments of the unapproved product are inappropriate for release under the personal importation policy because the article is available in the U.S.

FOI : No purging is required

KEYWORDS : PENTAMIDINE, NEW DRUG (NDA), LYPHOMED, FISONS, AIDS

/s/
ROBERT C. FISH

#4.10
//

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WPMAIL -DEC -ECHO
MAIL ALL-USERS  'IMPORT ALERT #66-50'
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DATE: OCTOBER 4, 1989

FROM: acting ASSOCIATE COMMISSIONER FOR REGULATORY AFFAIRS ~~(HFC-3)~~ HFC-1

SUBJ: IMPORT ALERT #66-50 "AUTOMATIC DETENTION OF PENTAMIDINE ISETHIONATE"

TO : IMPORT PROGRAM MANAGERS

INFO: ALL MAJOR FIELD OFFICES
RESIDENT POSTS

GCF-1 (A. LEVINE)
HFB-100 (T. BOZZO)
HFC-6 (CONTAMINANTS POLICY STAFF)
HFC-41 (S. LARSON)
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HFC-150 (DV. OF FED-STATE REL)
HFC-160 (R. SWANSON)
HFC-200 (OFFICE OF ENFORCEMENT)
HFC-210 (C. EVERLINE)
HFC-230 (E. BRISSON)
HFD-300 (D. MICHELS)
HFD-301 (S. YOUNG)
HFF-25 (E. STEELE)
HFF-26 (FIELD PROGRAMS BRANCH)
HFF-300 (OFF. COMPLIANCE)
HFF-310 (OFF. REG. GUIDANCE)
HFF-314 (IMPORT FOODS SECTION)
HFI-20 (PRESS OFFICE)
HFI-21 (PRESS OFFICE)
HFV-230 (EDWARD BALLITCH)
HFW-10 (OFF. LEG. AFFAIRS)
HFY-50 (J. HARTY)
HFZ-300 (W. GUNDAKER)
HPB-CANADA (B. WILLIAMS)

* * * * * * * * * * * URGENT NOTICE * * * * * * * * * * * * *

IMPORT ALERT 66-50 AUTOMATIC DETENTION OF PENTAMIDINE ISETHIONATE

PLEASE HOLD IMPLEMENTATION OF IMPORT ALERT 66-50 UNTIL THE TALK PAPER (T89) REFERENCED IN THE ALERT IS RECEIVED. YOU SHOULD RECEIVE TALK PAPER ON 10/5/89.

/S/
RONALD G. CHESEMORE

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.S
.END
OFF
>MAIL
Send, Read or Scan:  LINESIZE 300
Send, Read or Scan:  SEND
To:   ALL-USERS  'IMPORT ALERT #66-50'
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pcmail -echo
MAIL ALL-USERS SYS-RP 'IMPORT ALERT #66-50'

DATE: OCTOBER 5, 1989

FROM: ACTING ASSOCIATE COMMISSIONER FOR REGULATORY AFFAIRS (HFC-1)

SUBJ: IMPORT ALERT #66-50 "AUTOMATIC DETENTION OF PENTAMIDINE ISETHIONATE"

TO : IMPORT PROGRAM MANAGERS

INFO: ALL MAJOR FIELD OFFICES
RESIDENT POSTS

GCF-1 (A. LEVINE)
HFB-100 (T. BOZZO)
HFC-6 (CONTAMINANTS POLICY STAFF)
HFC-41 (S. LARSON)
HFC-50 (INTERGOV & IND AFF STF)
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HFY-50 (J. HARTY)
HFZ-300 (W. GUNDAKER)
HFB-CANADA (B. WILLIAMS)

* * * * * * * * * NOTICE RE PENTAMIDINE IMPORT ALERT * * * * * * * * * *

Continue to hold the subject document, because the agency has agreed to meet with members of the AIDS community this week to discuss the need for this alert. We will modify the talk paper now in draft to reflect those discussions. Your implementation of the alert, therefore, will continue to be dependent on your receipt of a talk paper, now likely after 10-10-89.

/s/
Ronald G. Chesemore

Lyphomed

Brian Tambi

Senior Vice President & General Manager
Ethical Pharmaceutical Division

October 5, 1989

Frank E. Young, M.D., Ph.D.
Commissioner of Food and Drugs
Food and Drug Administration
5600 Fishers Lane
HF-1, Rm. 1471
Rockville, Maryland 20857

Dear Dr. Young:

I am writing on behalf of Lyphomed, Inc. concerning a matter of serious concern to this company, i.e., recent evidence of sales in the United States of unapproved pentamidine. Of particular concern is a recent *New York Times* news report and *Health News Daily* of September 27, 1989 that suggest some individuals, groups, and organizations believe they can, consistent with FDA's policy and in compliance with applicable law, import unapproved pentamidine from other countries to compete with the approved Lyphomed product.

Certainly, the law does not allow such imports and, as we understand it, FDA policy would not permit such imports to avoid enforcement action. We are writing to you only because of our growing concern that the FDA's policy might change with respect to pentamidine and other pharmaceutical drugs marketed in the United States which have a similar status. If the FDA were considering changing its policy to allow importation of unapproved drugs to compete with legitimately approved and available drugs in this country, Lyphomed would like an opportunity to meet with you to explain the grave consequences such a change in policy would entail, its implications to the entire U.S. pharmaceutical industry, and other reasons why such a change in policy should not be adopted. If, on the other hand, present policy will not be changed, I am sure that the U.S. pharmaceutical industry will be greatly relieved if the FDA would take action that is appropriate to stop the illegal importation of drugs and discourage those who circumvent the law.

As you know, federal law strictly prohibits the importation of a new drug that has not been approved by the Food and Drug Administration, 21 U.S.C. & 331(d), 355(a). Also, by well-established precedent, it is illegal to sell an unapproved new drug after it has crossed state or national boundaries, 21 U.S.C. & 331(k). *See*, *e.g.*, *United States* v. *Articles of Drug*, 625 F.2d 665 (5th Cir. 1980). That law is clearly understood by all involved, and pharmaceutical companies make business plans based on the legitimate expectation that that law will be enforced.

The FDA's "personal use" policy, by its terms and by FDA's public interpretation, applies only to drugs that are not approved in the United States. The policy was, as we understand it, intended to permit, in very limited circumstances, the noncommercial importation for personal use of drugs not yet legally available in the United States.

It is true that there are many pharmaceutical drugs sold at a lower price in other countries. There are many reasons for such price differentials. One major reason is that the price of drugs in the United States reflects the tremendous costs associated with the research and development of drugs, not only the costs of research necessary to convince FDA that it is appropriate to approve such drugs for U.S. marketing but also the costs of Phase 4 and other follow-up research, all of which demand major financial investment and human resources. Pentamidine is a classic example of a drug that has made its way through a tremendously expensive R&D and regulatory process.

Lyphomed cannot support the viewpoint of a few who might argue that pharmaceutical drugs for treatment of AIDS should be provided at an artificially low price. As some AIDS patients and activists have asserted, that argument is shortsighted. It is undeniable that AIDS patients at risk of or suffering from PCP are also at great risk from other AIDS-related opportunistic infections and diseases — all of which are life-threatening. Thus, each such patient has a very personal stake in encouraging, rather than discouraging, pharmaceutical companies to invest in AIDS and AIDS-related therapies. Limiting the return on such investments is, accordingly, not good public policy or in the best interest of the national AIDS community.

As you know, a drug company takes a very large risk whenever it pursues development of any drug. In many cases, a drug company will work hard and expend millions of dollars in testing of drugs that fail the testing phases or falter to the extent that they are ultimately not approvable. Thus, in those very few cases in which the company is successful in bringing an important drug to market, there must be a return to the company that is sufficiently great to cover not only the costs attributable to that particular drug but also expected losses on those drugs that are not successful. Only such a system may be expected to motivate public investors to take the risk associated with drug development.

Lyphomed is in fact actively pursuing improvements of pentamidine in new formulation development, molecular modification in search of safer and more effective analogues, and in the technological development of superior delivery systems. Lyphomed also has other compounds under development for life-threatening and devastating diseases such as bone metastases, Paget's Disease, osteoporosis, cancer pain, etc. Lyphomed has absolutely no assurance that any of those products will ever be marketed. All of the expenditures on them could be lost. We need hardly emphasize that Lyphomed's AIDS and other research programs have substantial costs of clear relevance to the AIDS community that go beyond the costs directly associated with pentamidine.

There are, however, in this case very significant costs directly associated with pentamidine itself. The studies on the basis of which the NDA for aerosol pentamidine was approved cost approximately $20 million. As a condition of approval, Lyphomed was asked to perform, and has agreed to perform, phase 4 studies that Lyphomed estimates will cost approximately another $15 million. In addition, Lyphomed has been working with AIDS support groups nationwide to provide an interim patient assistance program for AIDS patients who need pentamidine with $2 million worth of this drug. (Note that the Lyphomed contribution is not conditioned in any sense on government matching funds.) Lyphomed has not received any funding from the government or government agencies. In fact, Lyphomed has been generous in providing funding and free drugs for a number of studies being conducted by the NIAID.

Moreover, Lyphomed must take into account the fact that the Orphan Drug Act exclusivity through June, 1996 granted to the aerosol product will be, as a practical matter, nearly illusory in slightly over two years when the Orphan Drug Act exclusivity on the injectable version of pentamidine runs out on October 29, 1991. Thereafter, generic companies can be expected to sell pentamidine, labeled as an injectable product. There is little doubt that some patients and physicians will simply use that product for the aerosol indication, despite the lack of labeling for that use. In other words, Lyphomed's NebuPent® (aerosol form) will lose exclusivity nearly five years before the legal term of exclusivity granted ends in 1996! In addition, Lyphomed is seriously concerned that, to date, Lyphomed has been given no confirmation that FDA will reject the attempts of a competitor, Fisons, to convince the FDA to approve a Fisons pentamidine product despite what we believe are the clear terms of the Orphan Drug Act's exclusivity provisions barring such an approval.

Pentamidine is, in any case, not the sole (or even the most commonly used) therapy available for its indicated uses. The current PCP prophylaxis market is divided among TMP/SMX (which is the drug used most often), Lyphomed's pentamidine product (NebuPent®), and Dapsone. Moreover, investigational protocols are looking at several new agents (i.e., Fansidar, Trimetrexate, Primaquine plus Clindamycin, DFMA, etc.).

Lyphomed was a pioneer in working with, and is continuing to work with AIDS support groups and with AIDS patients, to develop pentamidine's potential and to assure that it is used properly to save lives. In order to accomplish this important goal, however, Lyphomed has had to be -- and must continue to be -- a well-run business attractive to investors. Lyphomed, like other drug companies, in order to plan on developing AIDS drugs in the future, must have some assurance hat it will not face the clearly illegal importation of foreign products purchased from suppliers that have not had to undergo the expense of obtaining FDA approval.

Again, we are confident that FDA will, consistent with current policy, enforce the law vigorously with respect to illegal importation and sales of unapproved pentamidine and other pharmaceutical drugs. Should the Agency seriously contemplate another course, however, we would like an opportunity to meet with you to explain in more detail the effects of such a decision on, and the serious threat that such a decision would pose to, the U.S. research and development process, the U.S. pharmaceutical industry, and Lyphomed in particular.

Sincerely,

Brian Tambi

Brian Tambi
Senior Vice President & General Manager
Ethical Pharmaceutical Division

/rml

October 23, 1989

TO: John N. Kapoor, C.E.O., Lyphomed Inc.

FROM:
AIDS Action Council
AIDS Coalition To Unleash Power (ACT UP)/Chicago
AIDS Coalition To Unleash Power (ACT UP)/New York
American Association of Physicians for Human Rights (AAPHR)
American Foundation for AIDS Research (AmFAR)
Coalition for Compassion
Gay Men's Health Crisis (GMHC)
Human Rights Campaign Fund (HRCF)
Lambda Legal Defense and Education Fund
Mobilization Against AIDS
National Gay & Lesbian Task Force (NGLTF)
People With AIDS (PWA) Health Group
Project Inform
San Francisco AIDS Foundation

RE: Request for meeting with Lyphomed regarding NebuPent pricing

CC:
Louis Sullivan, M.D., Secretary of Health & Human Services
James Mason, M.D., Dr.P.H., Assistant Secretary of Health
Frank Young, M.D., M.P.H., Commissioner of Food & Drugs
Anthony Fauci, M.D., Director, National Institute of Allergy & Infectious Diseases
James Allen, M.D., National AIDS Program Office
Samuel Broder, M.D., Director, National Cancer Institute
June Osborne, M.D., Chairman, National Commission on the Acquired Immune Deficiency Syndrome
Sen. Edward Kennedy
Rep. Henry Waxman
Rep. Nancy Pelosi

* * *

As organizations and individuals devoted to the welfare of people with AIDS/HIV, we are pleased with the recent FDA approval of NebuPent as prophylaxis for pneumocystis carinii pneumonia (PCP). We commend Lyphomed for its initiative in investigating and seeking approval of this important therapy.

Approval for marketing of NebuPent by the Food and Drug Administration is only the first critical step toward accessibility and effective use. Informing physicians about the appropriate use of the drug is important. A third factor is price. We are deeply concerned that price may be a barrier to access for people with AIDS/HIV who could benefit from NebuPent but are unable to afford it.

We believe that the price of NebuPent in the United States should be reduced substantially. There is no adequate information regarding the factors that have led to the price that Lyphomed has set for Nebupent. We believe it is important for Lyphomed to discuss with us, the public, and policy makers why the price of NebuPent is as high as it is in the United States.

We understand that pricing is based on a broader calculus than simply the research and development costs associated with one particular drug. But the ultimate price must also be within reason and should not deny access to thousands.

High prices that are not justified by pharmaceutical companies marketing HIV-related therapies under the Orphan Drug Act will undermine support for this program, which we all feel is vital to HIV-related research as well as other diseases. It should also be noted that unreasonably high prices borne by the federal government for these therapies through Medicaid and other federal programs may spur calls for broader regulation of drug prices.

It is from this perspective that we ask that you meet with a small delegation of our choosing as soon as possible to discuss price-related access to aerosolized pentamidine. Please contact David Corkery at the American Foundation for AIDS Research, at 212/719-0033.

We look forward to your reply and a productive interaction.

The Los Angeles Coalition for Compassion is composed of:

Adolescent Treatment and Education Alliance
AIDS Coalition To Unleash Power (ACT UP)/Los Angeles
Alive and Kicking
AIDS Hospice Foundation
AIDS Services Foundation
Asian/Pacific AIDS Project
Being Alive/People With AIDS Coalition (PWAC)
Black and White Men Together
Blacks Living With AIDS
City of West Hollywood
Christopher Street West
Cara a Cara: A Latino AIDS Project
Gay and Lesbian Alliance Against Defamation (GLAAD)
Gay and Lesbian Community Services Center
Gay and Lesbian Latinos Unidos
Hay Institute
Los Angeles City AIDS Coordinator's Office
Municipal Elections Committee of Los Angeles
Metropolitan Community Church (MCC)/Los Angeles
Metropolitan Community Church (MCC) in the Valley
National Gay Rights Advocates
Northern Lights Alternatives
Positive Living for Us
Stop AIDS/Los Angeles
Some People's Children
United Spirit Church
West Hollywood Cares

ARNOLD & PORTER
1200 NEW HAMPSHIRE AVENUE, N. W.
WASHINGTON, D. C. 20036
(202) 872-6700
CABLE: "ARFOPO"
TELECOPIER: (202) 872-6720
TELEX: 89-2733

PARK AVENUE TOWER
65 EAST 55TH STREET
NEW YORK, NEW YORK 10022-3219
(212) 750-5050

1700 LINCOLN STREET
DENVER, COLORADO 80203
(303) 863-1000

DONALD O. BEERS
DIRECT LINE: (202) 728-4901

November 15, 1989

HAND DELIVERY

Mr. David Schulke
Special Committee on Aging
United States Senate
SD-G31
Dirksen Senate Office Bldg.
Washington, D.C. 20510

Dear David:

Enclosed, per our discussion yesterday evening, is the letter we sent to Terry Beirn. The letter provides a background on Lyphomed and pentamidine, answers some questions that Terry had raised, and includes a chronology. Also enclosed are reports that Lyphomed has received from its consultant concerning the availability of government reimbursement for pentamidine for indigent patients in various states. We understand that those reports are based on telephone conversations with State officials and that the consulting group is still in the process of getting hard copies of the applicable state regulations and guidelines.

The Lyphomed indigent program is based, as were the community clinical trials that it sponsored, on a partnership with local groups treating people with AIDS. Not-for-profit clinics or groups from around the country have contacted Lyphomed to be included in the program. Each was sent a questionnaire designed to elicit information concerning its status and the needs of the people it serves. When the questionnaires are returned, Lyphomed has begun shipping the drugs. The program, obviously, depends on the cooperation of those involved in clinics serving people with AIDS.

On the broader issue of the price of the drug, there appears to me to be a potential for working out a solution to that problem that would not deprive the company of funding necessary for additional research on pentamidine and related drugs. We would like, at this point, simply to avoid polarizing those concerned with the issue to the extent possible until the company can, in discussions with leaders of the AIDS support community, reach a consensus on how to proceed. (I enclose a copy of a request by a coalition of groups concerned with the AIDS crisis for a meeting with Lyphomed. Lyphomed is eager to have that meeting, which we expect will be scheduled fairly soon.)

Thank you for calling us about the hearing. I am sure we will be talking further as this matter progresses.

Sincerely,

Donald O. Beers

Enclosures

ARNOLD & PORTER
1200 NEW HAMPSHIRE AVENUE, N. W.
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DONALD O. BEERS
DIRECT LINE (202) 728-4901

November 8, 1989

Mr. Terry Beirn
Health Policy Advisor
Senate Committee on Labor
& Human Resources
Washington, D.C. 20510-6300

Dear Terry:

We are providing written answers to the nine questions about pentamidine which you faxed to me recently.

We have prepared the answers in accord with what we understand to be your intent in asking them, that is, to gather as much information as possible to give you a background on the issues. In some situations in which we have not been able to obtain documentation, we are simply providing Lyphomed's best recollection and understanding of events. Of some points we are very certain, since we have supporting documents.

As we view it, the development of pentamidine has been a remarkable Orphan Drug Act success story for which Congress frankly deserves a great deal of credit. In this letter, I explain why we think that is the case. That narrative description of events is followed by the questions and answers. Finally, in response to your request at out meeting on October 25, 1989, we have also included a chronology of Lyphomed's involvement with pentamidine.

PENTAMIDINE: AN ORPHAN DRUG ACT SUCCESS STORY

Lyphomed became involved with pentamidine in 1983. At that time, Lyphomed was a small company specializing in generic drugs. The company had, however, an expertise in the technique called "lyophilization," a process critical in the manufacture of pentamidine. In that year the Federal Centers for Disease Control ("CDC") was seeking a U.S. source of pentamidine. The original manufacturer of the drug, May & Baker, a Rhone-Poulenc subsidiary located in Great Britain, stopped supplying pentamidine to the CDC. CDC then began a search for a U.S. pharmaceutical manufacturer of pentamidine because it was important in the treatment of *Pneumocystis carinii* pneumonia ("PCP"), at that time a relatively rare infection that attacks patients with impaired immune systems. In 1983, the number of AIDS patients suffering from PCP was small -- reported by the National Organization for Rare Diseases ("NORD") to be between 300-600 patients -- and no U.S. drug manufacturer was interested in producing the drug. In early 1984, according to NORD, a medical emergency had developed as available supplies had run out. (*See* enclosed copy of NORD 1988 Corporate Award statement.)

As a U.S. Department of Health and Human Services News Release (October 24, 1984) (copy enclosed) makes clear, CDC and FDA "recruit[ed]" Lyphomed to make the drug commercially available in the U.S. Thus, Lyphomed was the only company that responded to the request from CDC, agreeing to produce 3,000 vials of the drug for CDC. Subsequently, at CDC's suggestion, Lyphomed took on the responsibility of becoming a commercial supplier of pentamidine. The company filed a New Drug Application (NDA) for pentamidine which was approved by the FDA. Pentamidine was designated as an orphan drug and seven years of exclusivity was granted to Lyphomed.

Lyphomed could not have taken on the costs associated with commercial production and marketing of what was essentially an "innovator" drug[1] without the exclusivity provided by the Orphan Drug Act. Certainly Lyphomed would not have been able to support research on the development on the aerosol version of pentamidine in the absence of Orphan Drug Act exclusivity.

Soon after it began marketing pentamidine in 1984, Lyphomed became aware that a few physicians were investigating the possibility that pentamidine could be used, in an aerosol form, to prevent PCP. The injectable use of pentamidine carries a high risk of serious side effects, making it inappropriate for prophylaxis. The use of the drug through the aerosol mechanism targeted directly to the lungs, however, showed a promise of avoiding those serious side effects and thus making pentamidine a reasonable choice for use in preventing PCP.

While some independent research was being done on this potential use of pentamidine, it became apparent that significant funding and human resources would have to be provided to determine whether or not this was a safe and effective use of the drug and, ultimately, to file an NDA with FDA and obtain approval of the new use. It is considerably more difficult and takes much longer to prove efficacy and safety for prophylaxis as opposed to treatment of a disease. Were there no Orphan Drug Act, no commercial enterprise could rationally make the enormous investment necessary to determine whether or not this proposed use and other innovative uses of the drug were appropriate. The testing and efforts applied to pentamidine between 1987-1989 cost more than $20 million and the costs are continuing to mount. No one could expect to recover that cost in a market in which prices were set by generic competitors whose costs do not include research and other costs associated with an innovator product.

---

[1] Marketing a generic drug (Lyphomed's business at that time) is considerably cheaper than marketing an innovator product. For one thing, the manufacturer of the generic drug does not need to bear the expense of educating physicians on how to use the drug. The innovator company has already done that. In fact, when Lyphomed first sold pentamidine, it initially distributed it in the way it distributed generic drugs. It became apparent, however, that simply making pentamidine available to pharmacists and hospitals did not ensure usage by physicians. As long as physicians did not know about the drug and did not know how to use it, it would not be used by physicians in treating patients who needed it. Lyphomed, therefore, took on the costs of educating physicians about the drug by hiring a detail force that was assigned to perform that function. Lyphomed was required to raise the price of pentamidine on two occasions, from approximately $25 per vial in 1984 to approximately $54 per vial, in 1986 -- a period of two years -- to pay for the necessary detail force and initial research efforts on aerosol pentamidine which commenced in 1984.

Because it had Orphan Drug Act exclusivity, Lyphomed was able to initiate and fund a series of sophisticated clinical trials and to fund a number of community based trials by raising the price at which injectable pentamidine sold to provide the necessary income to pay for these studies.[2] The rise in the price allowed Lyphomed, which did not have excess profits from its other operations to invest, to pay for the costs associated with the development of aerosol pentamidine. From a number of studies with various protocol designs, ultimately it was the carefully conducted and audited community research trials that showed that pentamidine was safe and effective for prophylaxis of PCP. Moreover, these trials produced a result that was unexpected. Statistical analysis determined that the use of one 300 mg. dose of pentamidine per month was more effective than the use of 150 mg. dosages of pentamidine twice per month. Thus, because this research, at thirteen centers involving seventy-three physicians, was directed and funded by Lyphomed, a more effective regimen was discovered to prevent the disastrous occurrence of PCP in AIDS patients.[3]

Because there was no patent for pentamidine, in a world without the Orphan Drug Act it is highly unlikely that anyone would have funded the necessary studies to show the effectiveness of aerosol pentamidine in preventing PCP. Because this statute was available, Lyphomed was able to pursue that research and to produce a potentially lifesaving and life extending therapy.

QUESTIONS AND ANSWERS

QUESTION 1.

Where did the "push" to develop Pentamidine for PCP come from? [CDC clearly played a role in obtaining the injectable product for treatment of acute disease; did any other government funded agency -- such as [illegible] -- take the lead in its development as a prophylaxis?]

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[2] Lyphomed ultimately raised the price on two additional occasions so that the final price was slightly under $100 per vial or roughly four times the initial, generic drug, price. Lyphomed did not charge that higher price initially and did not charge it until it became necessary to offset research and other costs. Lyphomed has not increased the price since August 1987.

[3] That single dose per month regimen is considerably less expensive than the bi-monthly regimen that many physicians had initially predicted would be effective. This is because a single dose regimen eliminates the cost of a second physician administration, the nebulizer expense, and other attendant health care costs during the month. In addition, a once-a-month dosage regimen is more convenient for patients and, therefore, enhances their compliance with this prophylaxis regimen.

It has been known since the 1950's that injectable pentamidine is effective in the treatment of PCP. In 1983, Rhone-Poulenc's British subsidiary, May & Baker, stopped the U.S. supply of pentamidine to the CDC. Lyphomed stepped in at the urging of the Federal government to manufacture pentamidine when no other company was willing to, in order to resolve a medical emergency for what was then a relatively small number of AIDS patients. As a result of this action and because of the company's continued efforts to improve pentamidine and develop other orphan drugs, Lyphomed has been publicly cited by NORD as "an outstanding model for the pharmaceutical industry as a developer of orphan drugs." (See enclosed 12/1/87 letter from NORD to Lyphomed.)

There is an alternative drug, trimethoprim/sulfamethoxazole (TMP/SMX), for the treatment of PCP that had proven to be safer than pentamidine in non-AIDS pediatric populations. In 1983, however, TMP/SMX was found to be more toxic than pentamidine in many AIDS patients. Injection of pentamidine also produced severe side effects in many patients. The need to develop and research new compounds was, therefore, compelling and obvious. Thus, the "push" began to develop alternative drugs, including other formulations of pentamidine, not only to treat PCP in AIDS patients but also to prevent it.

In 1984, Lyphomed began support of preclinical research by Drs. Bruce Montgomery and Robert Debs on aerosolized pentamidine targeted to the lung (i.e., aerosol use). Lyphomed committed to grants of drug and any other forms of support as required to support Drs. Montgomery and Debs in this research. Lyphomed has also supported the work of numerous other researchers in studies of aerosol pentamidine for treatment and for prophylaxis.

To our knowledge, Memorial Sloan Kettering Cancer Center reported preclinical work on aerosol delivery of pentamidine in abstract form, but has never published a peer reviewed article on this work. We are not aware of any one institution (public or private) that can fairly be described as having taken the "lead" in this research.

QUESTION 2.

Where was the basic research done that established pentamidine to be effective against the PCP "parasite"? Who funded it?

In 1957-1958, an injectable pentamidine trial in humans to treat PCP was carried out in Eastern Europe. Use of the drug was found to be effective. We have no information as to who may have funded this initial research. To our knowledge, no animal research was done prior to this human experiment.

QUESTION 3.

Did the idea for inhaling pentamidine to prevent PCP come from academia, government researchers, the developer of the nebulizer(s), or one of the companies? [Is there a clear first claim to the idea in the published literature?]

The idea of inhaled pentamidine to prevent PCP clearly came from academia. In 1972-1973, Dr. Robert Waldman from the University of Florida did initial toxicity testing of the aerosolized approach using the rodent model. He attempted to test the aerosolized protocol in the non-PCP-infected rat model. He was, however, unable to induce the PCP successfully and ultimately moved on to other areas of research. As Dr. Waldman explains, there was very little interest in treatment of PCP in 1973 and other matters were more pressing. Dr. Waldman's work appears in the American Review of Respiratory Disease, Volume 108, pp. 1004-6, October 1973. We understand that there was no funding from any source to support this work. To our knowledge, government researchers, developers of nebulizers, and other companies were totally uninvolved.

Our inquiries indicate that Dr. Waldman's work is the first claim to the idea in the published literature.

QUESTION 4.

When did each of the companies begin active clinical development of the product for prophylaxis? When did each begin development as an acute treatment?

** When was a U.S. IND filed, when was it okayed?
** When was the Canadian "IND" filed and okayed?
** Were there other significant clinical studies performed in other countries -- UK, France?

To our knowledge, at least four companies have filed for the orphan drug "designation" for aerosol pentamidine used for PCP. Of these four, Rhone-Poulenc and Zenith did not pursue any clinical research or product development in the U.S. We do not have complete information on Fisons Corp.'s activities. To our knowledge, Fisons has, however, done no research on the acute treatment of PCP. Fisons had conducted no research on PCP prophylaxis prior to their agreement with Memorial Sloan Kettering in mid-1987.

Preclinical studies on inhaled pentamidine supported by Lyphomed were started in 1984 by Drs. Bruce Montgomery and Robert Debs. As a result of encouraging data, Lyphomed supported Phase 1 trials applicable to both prophylaxis and treatment in 1986. These studies provided further encouraging results. Also in 1986, Lyphomed funded two separate treatment trials using the aerosol mechanism by Dr. John Conte and Dr. Bruce Montgomery.

In 1987, Lyphomed supported the San Francisco Community Consortium study for prophylaxis conducted by thirteen centers involving seventy-three physicians. At this time, Lyphomed also supported a pilot treatment study of inhaled pentamidine by Dr. Bruce Montgomery.

In March, 1988, Lyphomed commenced, along a parallel track to the community-based studies, two double blind, randomized and well-controlled studies. These were two major nationwide multi-center trials -- one for prophylaxis and one for treatment. Drs. Leoung and Montgomery, respectively, were the principal investigators.

Finally, data from the San Francisco Community Consortium study was gathered and analyzed to form the basis of Lyphomed's NDA submission along with a number of other independent supportive studies funded and supported by Lyphomed. The NDA was initially submitted in July, 1988, resubmitted in September, October and November, 1988. The NDA was considered by FDA to have been officially filed on November 14, 1988. FDA requested, however, that Lyphomed submit 18-month efficacy and safety data before the Agency would consider approval of the NDA. A Treatment IND was granted in February, 1989. A final filing was made in accordance with FDA instructions in April, 1989. NDA approval was given by FDA on June 15, 1989.

Initially, since injectable pentamidine was an FDA-approved drug marketed by Lyphomed, Dr. Montgomery assumed that an IND for inhalation therapy was not required. However, the FDA informed Dr. Montgomery in 1986 that an IND should be filed. Consequently, an IND was filed and approved immediately.

Lyphomed has not filed a Canadian "IND". Fisons must have done so, as it conducted a clinical trial in Canada. We do not have information concerning the dates of any Canadian IND obtained by Fisons.

Rhone-Poulenc has been licensed to utilize data obtained by Lyphomed and has used those data to seek approval of pentamidine for PCP prophylaxis in Canada and Europe.

To our knowledge, no significant clinical studies have been done in the United Kingdom or in France. Small scale studies have recently been done outside the U.S. using Lyphomed's study design (i.e., using the Lyphomed recommended nebulizer (Respirgard II), dose, and dosage regimen) with excellent results.

As to acute treatment, Lyphomed has just completed the largest double-blind, randomized well-controlled multi-center trial for acute treatment of PCP performed to date, utilizing the aerosol delivery system. In addition, Lyphomed is paying 51% of the cost of a number of NIH trials with pentamidine. To our knowledge, no other company or organization is investigating treatment of PCP with aerosol pentamidine.

QUESTION 5.

How many companies applied for an Orphan Drug designation for prophylactic usage of pentamidine? When did they apply? When was such designation granted?

As noted above, we understand that four companies -- Lyphomed, Fisons, Rhone-Poulenc, and Zenith -- at various times sought and were granted Orphan Drug Act "designation". We do not know whether others may have sought such designation unsuccessfully.

When Lyphomed was granted orphan drug status for pentamidine in October, 1984, the company believed the exclusivity granted by the law covered the pentamidine molecule and all potential uses for treatment and prevention of PCP. Fisons Corporation nevertheless applied for designation for use of aerosol pentamidine for prevention of PCP, apparently in a June 15, 1987 letter to FDA. That application was granted on October 5, 1987. As a consequence, Lyphomed made a similar application on November 2, 1987. Designation was granted to Lyphomed on January 12, 1988.

We do not have information on orphan drug designation dates for the other two designees.

The grant of designation does not, of course, suggest that the designee will ever obtain approval, nor does it confer exclusivity. It is the approval of the drug, combined with the designation, that confers orphan drug exclusivity.

QUESTION 6.

What guidance did each company receive from the FDA on criteria to be met in order to have a reasonable expectation of getting an NDA?

** Was this guidance consistent between 1985 and 1989?
** Was it consistent between the companies?
** Did FDA actively encourage a dose comparison trial design versus placebo control?

The guidance Lyphomed received from the FDA did not vary and was basically to provide scientifically valid evidence of efficacy and safety of inhal[illegible] pentamidine in the prevention of PCP. The FDA did not encourage, or discourage, any particular study design.

We have heard that representatives of Fisons have claimed that FDA told that company to do a placebo-controlled trial. We have no knowledge of the truth of those allegations, though in our experience FDA does not direct the type of trials to be conducted. Fisons may, however, have concluded that, for its specific nebulizer and dosage regimen, a placebo controlled trial would be necessary to establish safety and effectiveness.

In contrast, Lyphomed had already proved safety and efficacy of inhaled pentamidine with the use of the Respirgard II delivery system in the treatment trials that were performed in early 1987. What remained was to determine the optimal dose and dosage regimen for prevention of PCP. Since efficacy had already been established, Lyphomed, after consultation with scientists and medical advisors, decided that a placebo controlled study was neither needed nor appropriate. The optimal study design was determined, after careful assessment, to be a dose response trial in aerosol prophylaxis of PCP, even though Lyphomed's type of trial would require a year longer to complete than a placebo controlled trial.

QUESTION 7.

What evidence exists concerning nebulizer technology (and other delivery systems)? Is one nebulizer significantly better than another -- and how compelling is the evidence?

A problem with aerosol administration of pentamidine is that pentamidine is an airway irritant. If a medium sized particle nebulizer is used, some drug deposits in the alveoli (where PCP organisms are believed to be located). However, a substantial amount of drug deposits in the upper airways, resulting in serious airway irritation causing cough or bronchospasm (an asthma-like condition). Therefore, the higher the dose used with a medium sized particle nebulizer, the greater the chance of side effects. If the bronchospasm is severe, the bronchospasm may actually interfere with the delivery of drug to the alveoli and result in ineffective treatment.

Some experts believe that the use of a large particle nebulizer in the treatment content can be life threatening as it might result in ineffective treatment.

The published scientific evidence is compelling that, for treatment, a small particle nebulizer is needed for both optimal efficacy and safety. The best clinical results, both in treatment and in prophylaxis, to date have been reported with a small particle nebulizer -- the Respirgard II. Thus in both treatment and prophylaxis a small particle nebulizer (that minimizes bronchospasm while maximizing delivery to the alveoli where PCP is found) is the optimal device, based on clinical evidence in humans. Montgomery AB: "*Pneumocystis carinii* Pneumonia in Patients With the Acquired Immunodeficiency Syndrome: Pathophysiology, Therapy, and Prevention." *Seminars in Respiratory Infections*. 1989: (4); 102-110 (copy provided); Corkery KJ, Luce JM, and Montgomery AB: "Aerosolized Pentamidine for Treatment and Prophylaxis of *Pneumocystis carinii* Pneumonia: An Update." *Respiratory Care*. 1988: (33); 676-685 (copy provided). The state of the art in small particle nebulizers is the Respirgard II which is why the Respirgard II was used in all Lyphomed trials after careful evaluation.

QUESTION 8.

When did the respective companies become involved in Pentamidine's development as a PCP prophylaxis? By doing what? And spending how much?

** These costs need to be broken out for development associated with the injectable drug as an acute therapy versus prophylaxis, basic R&D versus clinical studies, manufacturing expense, distribution and promotion expenditures.

Lyphomed commenced its support of development of pentamidine for PCP prophylaxis in 1984. The initial funding was in support of preclinical research by Drs. Montgomery and Debs. Throughout 1985-1988 and continuing into 1989, Lyphomed has provided a stream of funds to other investigators, in addition to the continued support of Drs. Montgomery and Debs. The funds have been used to support both PCP prophylaxis and treatment trials with the aerosol formulation, as well as the technological development of new delivery systems, safer and more effective analogues, and improved drug formulations.

The entire pentamidine research and development program is continuing. Additional research to be funded by Lyphomed includes post-marketing studies required by the FDA such as additional large-scale primary and secondary prophylaxis trials, long-term animal aerosol toxicity studies, animal teratology studies, two-year carcinogenicity studies, and other studies. The expenses to date for all pentamidine studies are estimated at $23 million. The FDA required post-marketing studies are estimated to cost at least an additional $15-$20 million over a period of at least 3 years. Also, the company is supporting a pediatric trial of inhaled pentamidine and supporting 51% of a number of NIH aerosol trials in AIDS patients.

The total cost to be borne by Lyphomed is enormous and will be ongoing over the next 3-5 years. This expense extends beyond the period of market protection provided by the Orphan Drug Act exclusivity, which for all practical purposes expires in October 1991 -- i.e., in less than two years. Although Lyphomed has seven years of exclusivity for aerosol prophylaxis (June 15, 1989 thru June 15, 1996), once injectable pentamidine becomes available for generic marketing in October 1991, the company in effect loses nearly five years of this orphan drug "exclusivity."

QUESTION 9.

What messages and/or commitments were transmitted to each or all of the companies by the "communities" most interested in the rapid development of an effective PCP prophylaxis:

- AIDS Researchers and Clinicians?
- Regulatory officials?
- Community leaders and activists?

How were these messages sent and received -- is there a paper trail?

Many AIDS researchers and clinicians, regulatory officials, community leaders, and AIDS activists, came to know of Lyphomed as a result of the company's early leadership and involvement in the AIDS crisis. Lyphomed was the first company to fund community based research nationwide, particularly in the key health care centers treating AIDS patients in New York and San Francisco. A study funded by Lyphomed and performed by a San Francisco based community research group and other community physicians formed the basis of Lyphomed's New Drug Application for the use of aerosol pentamidine in PCP prevention.

The message and commitment from each group noted above was implicit -- all would work together to obtain the final goal, evidence of the optimum use of pentamidine for PCP prophylaxis and FDA approval of that use. The paper trail that exists is the product of that commitment -- the completed clinical studies, and ultimately, the full approval by the FDA of Lyphomed's New Drug Application for aerosol prophylaxis.

CHRONOLOGY OF LYPHOMED INVOLVEMENT WITH PENTAMIDINE

1983

1983	• Rhone-Poulenc stops supply of injectable pentamidine to U.S. market. CDC seeks domestic manufacturer for the drug.
	• CDC's request to U.S. companies to formulate and manufacture pentamidine was reportedly turned down.

1984

1984	• FDA and CDC urge Lyphomed to formulate and produce injectable pentamidine for treatment of PCP. Lyphomed agrees.
	• Once Lyphomed has successfully manufactured injectable pentamidine, CDC requests Lyphomed to take over distribution as well. Lyphomed agrees.
	• Lyphomed supports animal studies by Drs. Bruce Montgomery and Robert Debs with an aerosol form of pentamidine.
10/84	• Lyphomed obtains orphan drug status from FDA for injectable pentamidine used for treatment of PCP.
10/29/84	• Lyphomed NDA for injectable pentamidine approved by FDA for treatment of PCP.
End of October 1984	• Lyphomed markets injectable pentamidine at a price of $24.95 per vial.

1985

1985	• Lyphomed continues support of pentamidine pharmacokinetic studies and research on aerosol pentamidine.
1985	• Lyphomed begins organization of sales effort to educate physicians concerning pentamidine.
5/85	• Lyphomed sells injectable pentamidine at a price of $39.49 per vial.

1986

Early 1986	• Lyphomed informed that physicians are continuing to experiment with the use of pentamidine in animals in aerosol form; Lyphomed supports Phase 1 trials of aerosol pentamidine, the results of which would be useful for subsequent studies in treatment and prophylaxis.

1986	•	Lyphomed funds two separate PCP treatment trials in humans using the aerosol formulation, one trial conducted by Dr. Conte and one conducted by Dr. Montgomery.
	•	Lyphomed continues its effort to hire and train a detail force to teach physicians how to use injectable pentamidine safely and effectively.
7/86	•	Lyphomed sells injectable pentamidine at a price of $34.79 per vial.
1987		
1987	•	Lyphomed investment in aerosol pentamidine research gains in magnitude.
4/87	•	Lyphomed sells injectable pentamidine at $69.95 per vial.
7/87	•	Lyphomed sponsors community research initiative (San Francisco Community Consortium) to study PCP prophylaxis with aerosol pentamidine.
8/87	•	Preliminary results in 15 patients in Lyphomed-sponsored study conducted by Dr. Montgomery for treatment with aerosol pentamidine published in The Lancet (8/29/87); data are encouraging. Physicians begin calling Lyphomed to seek support for various pentamidine studies. Lyphomed agrees to supply drug in response to some of these requests. Lyphomed continues to sponsor aerosol pentamidine studies in humans for prophylaxis of PCP (Dr. Gifford Leoung/principal investigator) and for treatment of PCP (Dr. Bruce Montgomery/principal investigator). Lyphomed sells injectable pentamidine at $99.45 per vial.
10/4/87	•	Lyphomed sponsors symposium, chaired by Dr. Donald Armstrong, on pentamidine at Memorial Sloan Kettering. Results of research with aerosol pentamidine shared.
10/5/87	•	Lyphomed informed that Fisons Ltd. in collaboration with Dr. Armstrong and Memorial Sloan Kettering obtained FDA orphan drug designation for aerosol form of pentamidine for prophylaxis of PCP.
	•	Lyphomed was later informed that the Fisons-Memorial Sloan Kettering agreement was entered into as far back as June 1987.
11/2/87	•	Lyphomed applies for orphan drug designation from FDA for its aerosol form of pentamidine for prophylaxis of PCP.
1988		
1988	•	Lyphomed expenditures for pentamidine research accelerate substantially.
1/12/88	•	Lyphomed receives from FDA designation of orphan drug status for aerosol pentamidine used in the prophylaxis of PCP.
2/88	•	Lyphomed sponsors New York Community Research Initiative to study PCP prophylaxis with aerosol pentamidine.

4/18/88	•	Lyphomed receives corporate award from National Organization for Rare Disorders to honor Lyphomed for its willingness to "adopt" pentamidine when no other company stepped forward in 1983-1984 and for the company's continued pursuit of orphan drug research.
7/28/88	•	Lyphomed NDA for aerosol pentamidine prophylaxis of PCP submitted to FDA.
9/12/88	•	Lyphomed submits to FDA a nine-month efficacy data update for aerosol pentamidine used in prophylaxis of PCP.
11/14/88	•	Lyphomed submits additional data to FDA concerning efficacy of aerosol pentamidine for prophylaxis of PCP in a resubmission of the NDA.
12/22/88	•	Lyphomed meets with FDA reviewing division and Commissioner Young to discuss the Lyphomed NDA for the prophylaxis of PCP with aerosol pentamidine and the potential for a treatment IND for this indication. FDA requests that Lyphomed submit 18-month follow-up data from the PCP prophylaxis clinical trial. In response to this request, Lyphomed conducts a massive effort to locate the clinical trial participants, collect follow-up patient data, analyze the data, and submit the data to FDA.
1989		
2/6/89	•	FDA approves treatment IND for aerosol pentamidine for prophylaxis of PCP.
4/1/89	•	Lyphomed submits 18-month follow-up data to FDA from the PCP prophylaxis clinical trial.
5/1/89	•	FDA Advisory Committee on Anti-Infective Drugs reviews safety and effectiveness data of aerosol pentamidine for prophylaxis of PCP and unanimously recommends approval for this indication.
6/89	•	Lyphomed agrees to FDA requests to extensive post-marketing studies of aerosol pentamidine in the prophylaxis of PCP, including long-term animal and human studies, as well as large scale studies to determine whether aerosol pentamidine can be improved, either in safety or efficacy, for future uses.
6/15/89	•	Lyphomed NDA for aerosol pentamidine approved by FDA for prophylaxis of PCP. Seven years Orphan Drug Act exclusivity granted for aerosol prophylaxis of PCP.

* * *

I trust that you find this letter helpful in your review of this issue. Please feel free to call with any additional questions you may have.

Sincerely,

Donald O. Beers

Enclosures

Lyphomed

Brian Tambi

Senior Vice President & General Manager
Ethical Pharmaceutical Division

November 17, 1989

Frank E. Young, M.D., Ph.D.
Commissioner of Food & Drugs
Food and Drug Administration
5600 Fishers Lane, HF-1, Rm. 1471
Rockville, Maryland 20857

Re: Imports of Unapproved Pentamidine

Dear Dr. Young:

It has now been over a month since I wrote to you on October 5, 1989, expressing Lyphomed's grave concern about reports of imports of illegal pentamidine. In an October 16, 1989 issue of F-D-C Reports, a PWA Health Group spokesman is quoted as saying that the group will continue providing the drug until the need disappears. In addition, this spokesman is reported to have said that representatives of the Health Group "have spoken to FDA officials 'on a regular basis' and they have received 'no indication as yet [from the Agency] that there is a problem' regarding the Group's importation practices." To our knowledge, the FDA has made no public statement to conflict with that confident assurance that the law against illegal importation will not be enforced.

In my October 5 letter, I asked for an opportunity to meet with you if FDA were going to change its policy with respect to the importation of unapproved versions of approved drugs. The Agency's inaction has had the de facto effect of changing its policy. We are being informed by our sales representatives that pentamidine from unapproved foreign sources is widespread and is becoming increasingly available in the market and that customers are being openly solicited for purchases of unapproved imported pentamidine.

There will, in time, inevitably be a substantial "black market" for pentamidine and other important U.S. drugs that can be bought abroad at prices lower than those charged in this country. Extension of a "black market" to include unsafe and inefficacious versions of drugs is also inevitable. The safeguards inherent in FDA review of manufacturing and labeling of approved products obviously do not apply to black market drugs. The risks to patients from an FDA abdication of its responsibilities in this area are, we believe, substantial.

We are requesting an immediate meeting to discuss the serious issues involving the policy of allowing import into the United States of unapproved foreign version of drugs approved by the United States FDA. These foreign drugs are marketed at lower prices by foreign companies that do not conduct or bear the expense of research and regulatory costs associated with obtaining approval in this country. As you know, many millions of dollars were required to be expended by Lyphomed to obtain United States approval of aerosolized pentamidine for prophylaxis of PCP. In addition, the FDA required major post-approval trials that will cost many more millions of dollars. That money must, of course, come from somewhere. It must be provided from sales of the drug. Lyphomed is now feeling the impact of illicit pentamidine in lost sales revenue.

It is apparently being argued by some that the importation of unapproved versions for FDA-approved products should be permitted because it will have the effect of lowering the price of the American product. More recently, it is argued that enforcement of the law prohibiting such imports should be deferred so that some AIDS activists can threaten to increase (or resume[1]) imports if they are not satisfied with the indigent program funded by Lyphomed. This concept, that the law and law-enforcement is a bargaining chip to be utilized or withheld in this type of economic negotiation by activists is very troubling and is one that, we are certain, you would not endorse. The FDA has, of course, traditionally not involved itself in such economic bargaining at all.

In any case, if, by doing nothing, the FDA is perceived as signaling its strong support for the importation of unapproved foreign versions of FDA-approved drugs, either in "personal use" amounts or in larger amounts, the Agency will have made an important change in policy that will continue to have disastrous widespread effects. As you know, some promising AIDS drugs are not being developed by pharmaceutical companies because of, among other factors, the very unpleasant and intimidating political climate surrounding any AIDS pharmaceutical product. A policy of tolerating illegal imports that compete with approved U.S. AIDS drugs adds to the disincentive to AIDS research. The practical effects of inaction are, in any case, already extending beyond AIDS drugs. We have been informed by AIDS activists themselves that FDA's non-enforcement of the law in the face of pressure by some activists has already led to the importation of a variety of drugs that may be purchased more cheaply abroad.

We have always been impressed by the fairness and judgment with which FDA has dealt with the scientific and medical decisions that are a part of the drug approval process. The Food and Drug Administration has, of course, a second related role -- the enforcement of the laws that Congress has assigned it to enforce. The Agency has always earned the respect of those it regulates for its willingness to enforce those laws vigorously, without fear or favoritism. We must now ask that the FDA exercise its traditional leadership in law enforcement with respect to illegal imports of pentamidine. If the Agency is not prepared to do so, I renew my request for an opportunity to meet with you to discuss the seriousness of the effects of the Agency's continued inaction not only on our company but on the U.S. pharmaceutical industry in general and, in particular, on the hopes we all have for the research and development of pharmaceuticals that will respond to the AIDS crisis. If you believe it would be appropriate, we would also be pleased to meet with Dr. Sullivan and Dr. Mason.

Sincerely,

Brian Tambi

Brian Tambi
Senior Vice President & General Manager
Ethical Pharmaceutical Division

cc: Dr. Louis W. Sullivan
Dr. James O. Mason

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[1] We understand that representatives of some individual involved with this issue have promised to suspend their illegal imports while they decide whether they are satisfied with the Lyphomed indigent program. It is unclear whether any spokesperson could expect to represent all of those involved in illegal imports on this issue. In any case, the reports we receive do not reflect any such suspension.

Lyphomed

Brian Tambi

Senior Vice President & General Manager
Ethical Pharmaceutical Division

November 29, 1989

Senator David Pryor
Chairman, U.S. Senate Special
Committee on Aging
Russell Senate Office Building
Washington, D.C. 20510-0402

Dear Senator Pryor:

In a hearing before the Senate Special Committee on Aging on November 16, 1989 concerning prescription drug prices, statements and allegations were made about Lyphomed and its drug product pentamidine to which Lyphomed would like to respond in this letter. At the hearing, you stated that the hearing record would remain open for submissions during a ten-day period following the close of the hearing. In a discussion with the Committee staff, we were told that, in light of the intervening holiday, a submission received by December 1 would be timely. Accordingly, we respectfully request that this letter and its attachments be included in the hearing record.

Lyphomed would like to respond to the following seven issues that were raised at the November 16, 1989 hearing:

1. the illegal importation into the United States of unapproved pentamidine;
2. the profitability of orphan drugs;
3. the justification for price increases for pentamidine;
4. the Lyphomed indigent program;
5. the cost of nebulizers and of pentamidine administration;
6. European sources of pentamidine and their prices; and
7. Lyphomed's upcoming meeting with representatives of AIDS activist groups.

I. ILLEGAL IMPORTATION OF UNAPPROVED PENTAMIDINE

At the hearing on November 16, Derek Hodel testified concerning the illegal importation of unapproved pentamidine. (Section 301(d) and 505(a) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 331(d), 355(a), prohibit the import of unapproved drugs.) It is well known that Mr. Hodel is a major proponent of such illegal imports.

Lyphomed has indeed requested that FDA stop the illegal import of unapproved pentamidine. It is clear that the law does not permit such imports and Lyphomed is merely insisting on the proper enforcement of existing law in this area. We are enclosing herein copies of two letters that Lyphomed has sent to FDA Commissioner Young which address this problem (see Attachments 1 and 2).

If FDA does not enforce the law to prohibit these illegal imports of unapproved new drugs, it is predictable that a substantial commercial black market will develop in this country. Such a black market can present the kind of health risks discussed below (see issue 6). Moreover, the basis for pharmaceutical innovation in the United States will be severely undercut if unapproved foreign versions of U.S. drugs approved by FDA are permitted to enter the country.

Pentamidine presents an excellent example of the relationship between a country's policy toward drug costs and research. In 1984, Rhone-Poulenc's British subsidiary May & Baker refused to continue to supply the pentamidine needed to treat AIDS patients in the United States, apparently because the market was considered to be too small. We understand that many U.S. pharmaceutical companies also declined requests by the CDC to formulate, manufacture and supply the drug. According to authentic sources, a real "medical emergency" had developed at the time.

At the urging of the Centers for Disease Control, Lyphomed agreed to formulate and manufacture pentamidine for government distribtution and later accepted responsibility to seek FDA approval and supply pentamidine commercially. At that time pentamidine was used only as an injectable product to treat *Pneumocystis Carinii* pneumonia ("PCP)".

Subsequently, there was a great need to fund very expensive research to determine whether pentamidine might have an important new use -- as an aerosol product to *prevent* PCP. United States law had given Lyphomed market exclusivity for the injectable version of the product and the right to set the price of its drug in the market.

Lyphomed established the price of pentamidine in this country in order to pay for the need to establish a special physician sales force, a special marketing group and, since 1984, the escalating high costs of needed research. Ultimately, based on the results of five years of testing followed by nationwide clinical research, FDA concluded that aerosol pentamidine for PCP prophylaxis was safe and effective. It approved this new indication on June 15, 1989, after obtaining an agreement from Lyphomed to fund another estimated $15-20 million in post-approval trials over the next three to four years.

May & Baker, in the meantime, had funded no meaningful clinical trials (and may not have funded any trials at all) of aerosol pentamidine for prophylaxis. Its price remained low in Great Britain, where prices are controlled by the government, and its research effort was marginal to none. Thus, its research cost was also marginal. If Lyphomed had adopted (or had been required by government price regulation to adopt) the passive role in drug development adopted by May & Baker -- *i.e.*, if Lyphomed had refused to fund research and had declined to pay the cost of educating physicians about the safe use of the drug -- Lyphomed's price could be as low as May & Baker's price is today. *But no one would have produced the significant evidence that aerosol pentamidine, if used properly, can prevent PCP*. The life-extending benefits of aerosol pentamidine and the substantial cost savings to the U.S. Federal and State Governments, third party insurance institutions and the public from avoiding PCP would have been lost.

If the FDA does not enforce the law against import of cheaper unapproved foreign drugs from abroad, those importations may eventually have the effect of imposing European price controls on the American market. The ability of pharmaceutical companies to pay for needed research will be profoundly affected by that development. Moreover, that effect will not be the result of a considered decision by the Congress that the laws should be changed. It will, rather, be the product of the willingness of some to ignore the law and the unwillingness of the Executive Branch to take effective action to assure that the law is obeyed.

We believe that the FDA must take appropriate action under the current statutory regime to stop the illegal importation of drugs and to discourage those who circumvent the law.

II. THE PROFITABILITY OF ORPHAN DRUGS

In his testimony on November 16, Mr. Hodel stated that Congress, while enacting exclusivity for orphan drugs, intended that orphan drugs not be profitable. Mr. Hodel neglected to mention, however, that Congress well understood that seven years of marketing exclusivity meant potentially higher prices for the drugs approved under the Orphan Drug Act as well as greater and more predictable returns on investment to the company obtaining orphan drug approval. H.R. Rep. 153, 99 Cong., 1st Sess. at 6-7, reprinted in 1985 U.S. Code Cong. & Admin. News at 306. That was exactly the point of exclusivity -- providing the benefit of these market forces to encourage the pursuit of an important social goal such as orphan drug research and development. Exclusivity would, of course, be unnecessary if Congress did not contemplate that there would be potential profit in the sale of the drug. If there were no potential profit, no competitor would wish to share the market for the orphan drug. If no competitor wished to share the market, exclusivity would be unnecessary.

In this way, the exclusivity of the Orphan Drug Act is analogous to the patent laws, which limit competition and present a potential for higher prices for a period of time for certain products. Patents and periods of exclusivity have proven to be sound national policy in that they encourage research concerning, and the development of, new products and new indications for existing products.

III. EXPLANATION OF LYPHOMED'S PENTAMIDINE PRICE

In colloquy, Mr. Hodel stated that Lyphomed has not provided a justification to AIDS groups for the price increase of pentamidine. This statement by Mr. Hodel is not accurate.

In recent months, Lyphomed has met with a number of persons concerned with the AIDS crisis to discuss the costs that necessitated the rise in pentamidine's price, costs of educational programs for physicians in the use of pentamidine and research and development costs for aerosol pentamidine. In addition, Lyphomed publicly testified before Congress in 1988, providing a complete explanation of the development of the pentamidine price. Note that the price of pentamidine has remained constant since August 1987.

We have also enclosed a letter that was recently sent to Terry Beirn of the Senate Committee on Labor and Human Resources which discusses, among other issues, the price of pentamidine (see Attachment 3).

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IV. THE LYPHOMED INDIGENT PROGRAM

Mr. Hodel referred to the Lyphomed indigent program as a "media ploy." His characterization is completely inaccurate.

For many years, Lyphomed has been supplying pentamidine at no charge to a large number of patients under various non-regulatory physician protocols, as well as for regulatory clinical testing of the drug for use in prophylaxis and in PCP treatment. Upon FDA approval of the drug, Lyphomed announced a post-approval indigent program. As a result of discussions with many advisors, Lyphomed devised an innovative indigent program, the first of its kind in that it was designed to work with local nonprofit clinics at the community level in administering a program to distribute free pentamidine.

Mr. Hodel also stated at the November 16 hearing that his group was not aware of any distribution of pentamidine to non-profit community health centers under the Lyphomed indigent program. In fact, since the program was implemented on October 15, 1989, close to three hundred letters introducing the program have been sent to not-for-profit community based groups. Of these, approximately 50 have responded and 27 have qualified and received a total of over 2,500 free vials of pentamidine. Distribution has been nationwide. Furthermore, additional agreements with other community-based units nationwide are being processed. We wish to emphasize that this program was conceived, designed and implemented at the sole initiative of Lyphomed and not as a response to criticism.

V. THE COST OF NEBULIZERS AND DRUG ADMINISTRATION

At the November 16 hearing, Mr. Hodel discussed an HIV positive patient who was advised by medical professionals to purchase "a two hundred dollar" nebulizer in order to administer aerosol pentamidine prophylaxis to herself in her home. The nebulizer that is recommended in the labeling of Lyphomed's aerosol pentamidine product, the Respirgard II, in fact costs approximately $8.

We enclose for inclusion in the record (see Attachment 4) a copy of a survey performed by a group called "Patient Advocates for Necessary Treatment" relating to the physician and health care provider costs associated with administration of pentamidine for prophylaxis in San Francisco. The drug is sold at the same price to each provider and the Respirgard nebulizer cost is, as stated, relatively low. We do not know why the additional costs for administration of the drug are, in some cases, so high.

VI. EUROPEAN SOURCES OF PENTAMIDINE AND THEIR PRICES

At the November 16 hearing it was suggested that the pentamidine product from overseas is equivalent to Lyphomed's approved pentamidine product. There is really no proof to support that assertion.

The Lyphomed pentamidine product, in order to be approved by FDA, has been required to meet strict manufacturing and controls standards to ensure its safety, efficacy, purity, potency and stability. Every vial of pentamidine that Lyphomed produces must meet those exacting standards. The foreign product has not been required to meet those same FDA standards and has not been submitted for evaluation and approval of the FDA.

As you know, each drug manufacturer is required by U.S. law to satisfy applicable requirements to obtain FDA approval for its product, even though another company's version of the drug may have been approved previously. When drugs are imported without any FDA review, one cannot simply assume that the foreign manufacturer's product will be as safe or effective for its intended use as the FDA-approved drug. FDA review requirements are not mere technicalities. They serve a very important function -- to ensure each drug's safety and efficacy.

Moreover, Lyphomed has evidence that some of the illegally imported pentamidine is in bulk powder form to be compounded by local pharmacists and others, under potentially unsterile conditions, into a finished drug product. Such unsterile compounding can result in an unsafe and sub-therapeutic drug product reaching patients and thereby posing a significant health risk. Lyphomed has been able to obtain an injunction from a U.S. District Court in Texas to prohibit one such company from selling unapproved bulk pentamidine. (We enclose, as Attachment 5, a copy of an affidavit filed in that case addressing the health risk associated with compounding of bulk pentamidine.) However, Lyphomed cannot, as a practical matter, initiate separate court actions against all illegal importers. Rather, the law must be enforced by FDA to prevent the illegal imports in the first instance.

With respect to European drug prices, you heard at the November 16 hearing from two representatives of a Belgian consumer group that the reasons for lower pharmaceutical prices in

Europe are that European governments fix the prices of pharmaceuticals and attempt to restrict the prescribing practices of physicians to those drugs that are approved for reimbursement by the government. In contrast, we in the United States have traditionally operated in a free enterprise system which discourages such governmental price controls.

VII. LYPHOMED MEETING WITH AIDS ACTIVISTS

As Mr. Hodel mentioned at the November 16 hearing, Lyphomed has agreed to meet with representatives of the AIDS activist community in order to continue to discuss issues related to pentamidine. Lyphomed has spent much time and human resources in the last several months meeting with people concerned about AIDS in New York City and San Francisco and will continue, in the upcoming meeting in Washington, D.C. to be receptive to engaging in a dialogue about pentamidine.

We trust that these responses will help to clarify the information that was presented by Mr. Hodel at the November 16 hearing. It was suggested at the hearing that Lyphomed, which has devoted so much of its human resources and which has expended and is continuing to expend so much of its limited capital to work with community and other institutional researchers to develop aerosol pentamidine, pentamidine analogues, and other technologies for AIDS, has no "sense of social responsibility." That suggestion was, we believe you will agree, uninformed and unfair.

Sincerely,

Brian Tambi

Brian Tambi
Senior Vice President & General Manager
Ethical Pharmaceutical Division

Attachments [Special Committee on Aging staff note: Attachments have been placed in chronological order, where possible, in this Appendix.]

[Special Committee on Aging staff note: This document was submitted to the Committee by Lyphomed, Inc., as an attachment to Mr. Tambi's November 29, 1989 letter to Sen. Pryor.]

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF TEXAS

LYPHOMED, INC.
Plaintiff,
v.
PROFESSIONAL COMPOUNDING CENTERS OF AMERICA, INC., et al.
Defendants.

CIVIL ACTION NO. H-89-1792

AFFIDAVIT OF A. BRUCE MONTGOMERY, M.D.

A. Bruce Montgomery, M.D., makes the following statement:

1. I am currently Assistant Professor of Medicine at the State University of New York at Stony Brook, a position I have held since November 1988. I am also Director of the Medical Intensive Care Unit at that hospital.

2. I have been the principal investigator or co-investigator in many of the clinical studies evaluating the safety and efficacy of aerosolized pentamidine. In addition, I am the principal investigator in clinical research sponsored by the National Institute of Allergy and Infectious Disease ("NIAID") and LyphoMed, Incorporated ("LyphoMed") to study the safety and effectiveness of aerosolized pentamidine.

3. I have two investigational new drug applications under my name at the Food and Drug Administration, both concerning pentamidine salts.

4. I earned a Bachelor of Science degree in Chemistry from the University of Washington, Seattle, Washington in 1975 and an M.D. from the University of Washington in 1979.

5. I completed my internship and residency in Internal Medicine at the University of Washington from 1979-1982. From 1982-83, I was a Pulmonary Research Fellow at the University of Washington and from 1983-85 I was a Chest Fellow at the University of California in San Francisco.

6. I am Board Certified in Internal Medicine and Pulmonary Diseases and am a Diplomate of the National Board of Medical Examiners. I hold active licenses for the practice of medicine in the State of Washington, California, and New York.

7. From 1985 through November 1988, I served on the faculty of the University of California, San Francisco and the Cardiovascular Research Institute, Chest Service, San Francisco General Hospital.

8. I serve as a reviewer for the Journal of the American Medical Association, The European Respiratory Journal, the journal entitled Chest, the journal AIDS, and the Journal of Clinical Investigation.

9. I am a member of the Pneumocystis carinii Subcommittee of the Opportunistic Infections Committee of the AIDS evaluation and treatment evaluation units of the NIAID. I am a member of the Public Health Service Task Force on Anti-Pneumocystis Prophylaxis for Patients Infected with Human Immunodeficiency Virus.

10. I have presented papers and lectures to various professional organizations including the American Thoracic Society, American College of Chest Physicians, Interscience Conference on Antimicrobial Agents and Chemotherapy, and the 1988 International Conference on AIDS.

11. I am the author or co-author of more than 25 published articles and more than 20 published abstracts relating to pulmonary medicine, particularly the treatment of AIDS patients and the treatment of Pneumocystis carinii pneumonia ("PCP"). A more detailed description of my professional qualifications and a list of my publications is contained in my Curriculum Vitae, which is attached.

12. Because of my education, training and experience, I am knowledgeable about the treatment of AIDS patients, particularly those suffering from pulmonary diseases such as PCP, and treatment of those patients with pentamidine isethionate.

13. PCP is a severely debilitating pneumonia in which lung tissue is destroyed, at a particularly rapid pace in immunocompromised patients such as those with

AIDS, producing an inability to breathe and supply oxygen to the body tissues, and, if not appropriately treated, finally death.

14. I have been asked to address the potential problems that may be associated with the administration of pentamidine that has been compounded by pharmacists from bulk pentamidine. Ethical drug manufacturing requires multiple steps to ensure quality, purity, and sterility. Compounding in a pharmacy, not subject to those safeguards, may result in administration of drugs that contain impurities, degradation products, or microbial contaminants.

15. One must be particularly concerned about the possibility of microbial contamination in products compounded by pharmacists. Open air measurement of bulk drug on scales allows a strong probability of microbial contamination. The subsequent dissolving of the drug in a water solution for later use increases the danger. Bacteria can grow creating a concentrated solution of bacteria in the drug in a matter of hours.

16. Heat sterilization of pentamidine water solution is not possible because heat would destroy the drug and the remains of dead bacteria can still cause severe asthma-like reactions when inhaled or shock when injected. Other methods of sterilization, such as filtering, are not foolproof when performed by small scale operations. They require laminar flow hoods and large sterile laboratories.

17. There are two areas of concern using bulk drug pentamidine isethionate because there are two routes of administration of the drug, intravenously and by aerosol. In either case, the drug will be administered most often to patients with AIDS or with pre-AIDS conditions. These patients are particularly vulnerable to the risks from contaminated drug because their immune systems are compromised by their disease.

18. Administration of pentamidine by injection to treat PCP exposes the patient to the risk of sometimes severe side effects associated with systemic circulation of the drug. That is a risk that is justified by the benefit, i.e., clearing of the infection, which can be fatal if left untreated. If the

pentamidine injected into the patient contains impurities, the patient is placed at additional risk from the unknown effects of the impurities, with no corresponding benefits. There is no justification for exposing these often very sick patients to that additional risk.

19. If the pentamidine is not sterile, if it carries with it some infectious agent, its administration to AIDS patients suffering a bout of PCP could well be fatal. Because an AIDS patient has a severely debilitated immune system, the patient lacks the ability to fight off any infection that might be introduced by the non-sterile product.

20. The effect on humans of unpure pentamidine given by the aerosol route is just not known. No deliberate testing has been done. However, it is quite conceivable that impurities could cause asthma-like symptoms or progressive lung scarring.

21. The effect of bacterial contamination on aerosol preparations is well known. Aerosol-borne lung infection has been well described. In the early 1970s, many deaths were attributed to contaminated respiratory care equipment that led to the direct innoculation of bacteria into the lungs of patients.

22. Although Pneumocystis carinii is the most common pneumonia in AIDS patients, typical bacterial pneumonias also occur frequently if the immune system is severely damaged. These bacterial pneumonias can cause great suffering and can in fact be fatal to AIDS patients.

23. One of the common bacterial pneumonias caused by contaminated equipment in the past is caused by pseudomonas, a bacteria that can grow easily in water alone, the substance used to dissolve pentamidine. Furthermore, pentamidine does not have any ability to kill pseudomonas.

24. The use of impure compounded pentamidine isethionate is a true menace to AIDS patients. To turn a breakthrough AIDS drug into a potential threat to the health of the user is a perverse act.

25. From my experience in treating AIDS patients, I understand that information is communicated very rapidly in that patient group by an extensive network of informal and formal communications. Information received by patients through this network can often influence the beliefs of AIDS patients, irrespective of information received from physicians. If one patient suffers an adverse event from compounded pentamidine, and other patients, upon hearing through this network that this drug may be harmful, refuse to use pentamidine, thousands will die needlessly and painfully, choking to death from pneumonia.

I declare under penalty of perjury that the foregoing is true and correct.

A Bruce Montgomery MD
A. Bruce Montgomery, M.D.

Executed on 21 May 1989

CURRICULUM VITAE

May, 1989

Alan Bruce Montgomery, M.D.

PERSONAL DATA

Date of Birth:	May 18, 1953
Place of Birth:	Seattle, Washington
Citizenship:	USA
Marital Status:	Married, one child
Social Security Number:	536-48-8824
Current Home Address:	25 Conscience Circle, Setauket, NY 11733
Current Work Address:	Pulmonary Disease Section Department of Medicine Health Science Center T17 Room 040 State University of New York Stony Brook, NY 11794

EDUCATION

Undergraduate:	University of Washington, Seattle, WA. 1975, B.S. in Chemistry
Medical School:	University of Washington, Seattle, WA. 1979, M.D.

POSTGRADUATE TRAINING

Internship and Residency in Internal Medicine: 6/79 to 6/82, University of Washington, Seattle, WA
Pulmonary Research Fellow: 6/82 to 6/83, University of Washington, Seattle, WA
Chest Fellow: 7/83 to 7/85, University of California, San Francisco, CA

HONORS

Undergraduate: Magna cum Laude, Outstanding Chemistry Major (Merck Award), Phi Beta Kappa.
Graduate: Alpha Omega Alpha honor medical society.

CAREER POSITIONS

6/85 to 6/87 Instructor of Medicine University of California, San Francisco and Cardiovascular Research Institute, Chest Service, San Francisco General Hospital.

6/87 to 11/88 Assistant Professor of Medicine in Residence University of California, San Francisco and Cardiovascular Research Institute, Chest Service, San Francisco General Hospital.

11/88 to now Assistant Professor of Medicine, Director of the Medical Intensive Care Unit, Pulmonary Disease Section, Department of Medicine, State University of New York, Stony Brook, NY

FEDERAL GOVERNMENT PUBLIC ADVISORY COMMITTEES

1/88 To now Member Pneumocystis carinii subcommittee of the opportunistic infections committee of the AIDS evaluation and treatment evaluation units of the NIAID and protocol chairman of AETU protocol 040: A controlled trial comparing the efficacy of aerosolized pentamidine and parenteral/oral trimethoprim-sulfamethoxazole in the treatment of Pneumocystis pneumonia in AIDS.

2/89 To now Member of Public Health Task force on Anti-pneumocystis prophylaxis in patients infected with Human Immunodeficiency Virus

FOOD AND DRUG ADMINSTRATION IND'S FILED

1985	Dexamethasone for Acute Mountain Sickness
1986	Aerosolized Pentamidine Isethionate
1987	Indium 113
1989	Aerosolized Pentamidine Gluconate

LICENSES AND CERTIFICATIONS

Medical License, Washington, 1979
Medical License, California, 1983
Medical License, New York, 1988
National Board of Medical Examiners, 1980
American Board of Internal Medicine, 1982
American Board of Internal Medicine, subspecialty certification in pulmonary,1986

PROFESSIONAL ACTIVITY

SERVICE TO PROFESSIONAL PUBLICATIONS

1985-now	Chest	Ad hoc referee
1987-now	Journal of American Medical Association	Ad hoc referee
1988-now	The European Respiratory Journal	Ad hoc referee
1988-now	AIDS	Ad hoc referee
1989-now	Journal of Clinical Investigation	Ad Hoc referee

SCIENTIFIC AND PROFESSIONAL MEETINGS ATTENDED

American Thoracic Society., 1982 , 1983 (paper),
1984, 1985 (papers), 1986 (papers), 1987 (papers), 1988 (papers), 1989 (lecture and paper)
American College of Chest Physicians, 1983 (paper), 1987 (lecture), 1988 (lecture)
Interscience Conference on Antimicrobial Agents and Chemotherapy 1987 (paper), 1988 (paper)
International Conference on AIDS, 1988 (papers)

INFORMAL TEACHING

1986-1988	Attending in Medical Intensive Care Unit, Chest Service, and Chest Clinic at San Francisco General Hospital
1985-1988	Noon conferences for housestaff at San Francisco General Hospital
1986-1988	Pulmonary disease conferences for medical students onFamily Medicine

TEACHING AIDS PREPARED

1986-1988	Weinberg PF, Luce JM, Boushey HA, Montgomery AB, eds. Introduction to Pulmonary and Critical Care Procedures. Division of Pulmonary Diseases, University of California, San Francisco (Handbook for new clinical fellows).

TEACHING,FORMAL SCHEDULED CLASSES FOR UCSF AND SUNY STUDENTS

Academic Year	Course	Position	Students	Hours
1986-1988	Medicine 132A (ICM)	Section Leader	4	16
1985-1988	Medicine Senior Year Pathophysiology Course	Lecturer	8	1
1986-1988	Medicine 111	Lecturer	20	3
1988- now	Respiratory physiology lectures	Section Leader	20	3

POSTGRADUATE COURSES SPONSORED BY UCSF

1985-1988	Pulmonary and Critical Care Medicine: A Practical Approach	lecturer

INVITED LECTURES

1986-now	Various lectures at Northern California hospitals
1987	Westmead Hospital, Syndey Australia
1987	Fairfax Hospital, Melbourne Australia
1988	INSERM, Hopital Claude Bernard, Paris France
1988	SUNY, Stonybrook, NY
1988	Van Etten Hospital, NY, NY
1988	Charity Hospital, New Orleans
1988	St. Mary's Hospital, Long Beach, CA
1988	UCSD, San Diego, CA
1988	USC, Los Angeles, CA
1988	Mt. Sinai Hospital, New York, NY
1988	Providence Hospital, Seattle,WA
1988	Harborview Hospital, Seattle, WA
1988	Yale University, New Haven, CT

PUBLICATIONS:

ARTICLES

Moore TA, Montgomery AB, Kwiram AL. Triplet electronic structure and photoreactivity of 8-methoxypsoralen. Photochemistry and Photobiology 24:83-86, 1976.

Stillman PL, May JR, Meyer DM, Rutala PJ, Veach TL, Montgomery AB. A collaborative effort to study methods of teaching physical examination skills. J Medical Education 56:301-307, 1981.

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Huchon GJ, Montgomery AB, Lipavsky A, Hoeffel JM, Murray JF. Respiratory clearance of aerosolized radioactive solutes of varying molecular weight. Journal of Nuclear Medicine 28:894-902, 1987.

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Debs RJ, Straubinger RM, Brunette EN, Lin JM, Lin EJ, Montgomery AB, Friend DS, Papahadjopoulos DP. Selective enhancement of pentamidine uptake in the lung by aerosolization and delivery in liposomes. Am Rev Respir Dis 135:731-737, 1987.

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Montgomery AB, Debs RJ, Luce JM, Corkery K, Turner J, Brunette EN, Lin ET, Hopewell PC. Aerosolized pentamidine as sole therapy for *Pneumocystis carinii* pneumonia in patients with acquired immunodeficiency syndrome. Lancet 2:480-483, 1987.

Debs RJ, Montgomery AB, Brunette EN, DeBruin M, Shanley JD. Treatment of Murine Cytomegalovirus Lung Infection by Aerosol Administration of Antiviral Agents. J Inf Dis 1988 In press.

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Luce JM, Montgomery AB, Marks JD, Turner J, Metz CA, Murray JF. Ineffectiveness of high dose Methylprednisolone in preventing parenchymal lung injury and improving mortality in septic shock. Am Rev Respir Dis 138:62-68, 1988

Debs RJ, Fuchs HJ, Philip R, Montgomery AB, Brunette EN, Liggitt D, Patton JS, Shellito J. Lung-specific delivery of cytokines induces sustained pulmonary and systemic immunomodulation in rats. J of Immunology 1988; 140:3482-3488.

Corkery KJ, Luce JM, Montgomery AB. Aerosol Pentamidine for treatment and prophylaxis of *Pneumocystis carinii* pneumonia: an update. Respiratory Care 1988; 33:676-685.

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Clement M, , Turner J, Edison R, Luce J,Montgomery B,Hopewell P. Corticosteroids as adjunctive therapy in severe Pneumocystis carinii pneumonia. A retrospective study. Am Rev Respir Dis 139:A560, 1989.

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EXTRAMURAL SUPPORT

1984-1988	Research support through Pulmonary Vascular SCOR HL-19155
1983-1986	Research support from the Upjohn Company
1987-1989	Research support from LyphoMed, INC
1988-now	Research support through NIAID ATCG contract

[Special Committee on Aging staff note: This document was submitted to the Committee by Lyphomed, Inc., as an attachment to Mr. Tambi's November 29, 1989 letter to Sen. Pryor.]

In October, LyphoMed announced it will provide pentamidine for aerosolized use free of charge to physicians and clinics for their patients without health insurance. A PMA Health Group spokesperson characterized LyphoMed's action as directly helping indigent patients, but continuing to maintain its inflated wholesale price of $99.54 for insured and cash-only patients, which ultimately translates into higher insurance premiums and increased taxes for Medicaid programs. Physician information regarding LyphoMed's A-P program, contact Rick White, Senior Product Mgr., 1-800-888-7704, Ext. 1772.

INTRODUCTION TO SURVEY

This survey does not claim to be complete nor comprehensive as to total number of people using Aerosolized Pentamidine in San Francisco. In most cases, the figures provided are accurate; in some instances the figures are expert estimates. Readers should bear in mind that some individuals do their A-P treatments in their home, and are therefore difficult to tabulate for purposes of this survey.

The survey is presented to give an indication of the extent of A-P use in San Francisco, as well as anticipating future use as individuals who are at risk for PCP seek early intervention prophylaxsia; to indicate the variations in current cost of A-P treatment in San Francisco; and to indicate the population receiving A-P under the federal subsidy program.

(EDITOR'S NOTE: PATIENT ADVOCATES FOR NECESSARY TREATMENT (PANT) offers information, points of view and increased awareness concerning HIV treatment and patient care issues for people infected with HIV, health care providers and concerned others. Nothing in this newsletter nor survey should be regarded as providing medical advice or endorsement of any particular treatment. It is provided for informational purposes only.)

PANT wishes to acknowledge the cooperation and assistance of health care professionals throughout San Francisco for their generous sharing and input.

SURVEY OF AEROSOLIZED PENTAMIDINE USE IN SAN FRANCISCO COUNTY (AS OF SEPTEMBER 30, 1989)

FACILITY	(1) TOTAL PATIENTS RECEIVING A-P	(2) COST PER TREATMENT	(3) PATIENTS ENROLLED IN FEDERAL SUBSIDY PROGRAM
San Francisco General Hosp. 995 Potrero Avenue San Francisco, CA 94110 (415) 821-8012	140	$251.28	51
Pacific Presbytarian Medical Center 2300 California St. San Francisco, CA 94115 (415) 923-3438	533	$280.10	42
Mt. Zion Hospital 1600 Divisadero Street San Francisco, CA 94155 (415) 885-7386	256	$261.46	46

FACILITY	(1) TOTAL PATIENTS RECEIVING A-P	(2) COST PER TREATMENT	(3) PATIENTS ENROLLED IN FEDERAL SUBSIDY PROGRAM
Ralph K. Davies Med. Ctr. Castro & Duboce Streets San Francisco, CA 94114 (415) 565-6226	900	$267.10	0
Children's Hospital 3700 California Street San Francisco, CA 94118 (415) 750-6547	130	$207.96	1
St. Luke's Hospital 3555 Army Street San Francisco, CA 94118 (415) 647-6565	67	$182.00	0
St. Francis Memorial Hosp. 900 Hyde Street San Francisco, CA 94109 (415) 775-4321 Ext. 4763	115	$265.94	0
St. Mary's Hospital 450 Stanyan Street San Francisco, CA 94117 (415) 750-5713	35	$280.00	0
University of California San Francisco Medical Center 400 Parnassus St., 5th Floor San Francisco, CA 94143 (415) 476-3961	400	$175.00	2
Kaiser Permanente 2280 Geary Blvd. San Francisco, CA 94115 (415) 929-2871	558	*	0
Veteran's Administration 4150 Clement Street San Francisco, CA 94121 (415) 221-4810, Ext. 3763	120	**	0
Alan Levin, M.D. 450 Sutter Street, #1138 San Francisco, CA 94108 (415) 788-4535	60	$200.00	0
Sutter Street Surgery Ctr. 450 Sutter St., #600 San Francisco, CA 94108 (415) 981-1666	10	$265.00	0
Marcus Conant, M.D. 1635 Divisidero Street Suite 600 San Francisco, CA 94117 (415) 923-1333	150	$215.00	0

FACILITY	(1) **TOTAL PATIENTS RECEIVING A-P**	(2) **COST PER TREATMENT**	(3) **PATIENTS ENROLLED IN FEDERAL SUBSIDY PROGRAM**
Stonewall Medical Group **45 Castro Street** **San Francisco, CA 94114** **(415) 565-6501**	10	$245.00 ***	0
Caremark Connection **4052 18th Street** **San Francisco, CA 94114** **(415) 864-6960**	40	$250.00	0
Virx **655 Sutter St., Ste. 600** **San Francisco, CA 94102** **(415) 474-4440**	10	$185.00	0
Thomas Schiller, M.D. **45 Castro Street, Ste. 232** **San Francisco, CA 94114** **(415) 621-3371**	51	$212.00	0

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(1) Total number of patients receiving Aerosolized Pentamidine (A-P) per month including those covered by private health insurance, HMOs, PPOs, MediCal and MediCare; patients enrolled in federal subsidy program; and patients receiving A-P through clinical trials.

(2) Cost per treatment refers to 300 mg. of pentamidine diluted in solution, nebulizer and all other facility/technician charges associated with administration.

(3) Patients enrolled in federal subsidy program do not pay for drug or nebulizer, but are responsible for facility or technician charges, if any.

* Kaiser Permanente patients not charged for A-P, irrespective of whether their Kaiser health plan includes prescription benefits. Therefore, a cost per treatment is not available. Note that Kaiser Permanente recently acquired French Hospital in San Francisco; therefore all A-P treatments for both Kaiser & French Hospital are combined at Kaiser facility.

** Veteran's Administration Hospital provides health care free of charge for those veterans who have served in the military. Therefore, a cost per treatment figure is not available.

*** Includes $150.00 charge billed separately by LifeSource for cost of pentamidine and nebulizer.

PANT INVITES LETTERS, ARTICLES AND OTHER RELEVANT INPUT FROM OUR READERS.
PLEASE SEND TO:

Morgan Fine
PANT
4302 19th Street
San Francisco, CA 94114

DAVID PRYOR, ARKANSAS, CHAIRMAN
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United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

December 8, 1989

Mr. Derek Hodel
Executive Director
People With AIDS Health Group
4th Floor
31 West 26th Street
New York, NY 10010

Dear Mr. Hodel:

Thank you for your participation in the November 16 hearing of the Senate Special Committee on Aging, investigating the impact of and possible solutions for rapidly rising prescription drug prices in the United States.

Your testimony, and the information you provided to Committee staff prior to the hearing itself, provided a vital link in the Committee's study of the impact of high prescription drug prices in the United States. In fact, I was persuaded by your testimony to write the attached letter to the Federal Food and Drug Administration (FDA), seeking their analysis of a specific proposal that would help to make a lower priced-aerosolized pentamidine product available in the U.S. market. I would also like to know your feelings about the proposal I made to the FDA.

For your information, I have also enclosed copies of the Committee staff reports from both the July 18, 1989 hearing on this subject, and the November 16 hearing just concluded. I hope you find this information as helpful and interesting as yours was for the Committee and its staff.

Once again, thank you for your time and assistance, and please accept my best wishes for a peaceful and relaxing holiday season for you and your loved ones.

Sincerely,

David Pryor

David Pryor
Chairman

Enclosures
DP:dgs

DAVID PRYOR, ARKANSAS, CHAIRMAN

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United States Senate
SPECIAL COMMITTEE ON AGING
WASHINGTON, DC 20510-6400

December 8, 1989

The Honorable Frank E. Young, M.D.
Commissioner, Food and Drug Administration
Room 14-71 Parklawn Building
Rockville, MD 20857

Dear Dr. Young:

I am writing to request your analysis and advice regarding a legislative proposal that would facilitate the approval of lower priced prescription drug products for "orphan" diseases.

As you know, the Federal Food and Drug Administration may designate a prescription drug as an "orphan" drug, and, concomitant with approval of the drug for U.S. marketing, grant exclusive marketing rights to the manufacturer of that product for a period of seven years. Observers of the prescription drug industry have given Congress high marks for granting FDA this authority, which is credited with spurring the development of badly-needed new drugs for small populations of Americans who would otherwise receive less safe or less efficacious treatment.

During the course of hearings by this Committee aimed at finding solutions to the rapidly escalating cost of prescription drugs, I learned that the FDA has granted "orphan" drug status for pentamidine, manufactured by Lyphomed, for marketing in an aerosolized form if it is used in a specific nebulizer device. Another firm, Fisons, Inc., has reportedly developed a different nebulizer technology for the identical use. I further understand that the aerosolized Fisons drug product, under the terms of the Orphan Drug Act, cannot be marketed for the same use in the United States until the period of exclusivity granted Lyphomed has expired.

It is also my understanding that FDA, even after many clinical trials involving both products, has received no data demonstrating that either drug product is superior to the other in terms of safety or efficacy for the approved aerosolized use. However, the "FisoNeb" nebulizer achieves this apparently equivalent effect while using only about 40% as much pentamidine per month of treatment as the nebulizer approved for administration of the Lyphomed product. In view of the high cost of pentamidine treatment, Fisons' technology represents a very significant cost saving for HIV-infected people.

I am concerned that Congress has inadvertently created a situation in which a badly needed product, associated with a more efficient, cost-saving delivery system, may be prevented from competing in the U.S. market. At the same time, it seems clear that Lyphomed has abused its protection from competition under the law, exploiting the opportunities presented by the Orphan Drug Act to raise its price for pentamidine by almost 400% since 1984.

It appears this situation cannot be resolved under the narrow terms of current law. FDA is not authorized by the Act to approve a second firm's request to market an "orphan" drug for an identical medical purpose, even when presented with evidence of advantages resulting from a substantially different drug delivery system.

Therefore, I would be grateful to receive FDA's perspective on a technical change to the Orphan Drug Act which would authorize FDA to approve a second manufacturer's orphan drug for a period of "shared" (possibly coterminous) exclusivity with the first approved orphan product, when it is approved for the same use in conjunction with a delivery system of substantially superior safety, efficacy, or lower cost to the patient/user. A firm which violated the terms of their grant of "shared" exclusivity under this provision -- for example, by raising the price of their product so the substantial cost advantage which earned them "shared" exclusivity disappeared -- could have their "shared" exclusivity privilege revoked by FDA.

This approach is intended to preserve the incentives of the Orphan Drug Act, while balancing them with the virtues of competition under circumstances where another firm has taken a risk and has developed a clearly superior technology. Moreover, this incremental approach to documented abuses of the Orphan Drug Act is consistent with this February 1989 recommendation of the National Commission on Orphan Diseases:

> "...the Commission is very concerned that the potential for abuse of the incentives in the Orphan Drug Act will threaten its future. The Commission therefore urges that if abuses are clearly documented, Congress consider limited corrective legislation."

I would appreciate receiving the Agency's response by the end of January, 1990. Please have your staff contact David Schulke at 224-5364 to discuss this proposal.

Sincerely,

David Pryor
Chairman

DP:dgs

Bruce Montgomery, M.D.
921 Arlington Road
Redwood City, CA 94062

January 15, 1990

Senator David Pryor
Chairman, U.S. Senate Special
Committee on Aging
Russell Senate Office Building
Washington, D.C. 20510-0402

Dear Senator Pryor:

I am writing to you to discuss the drug pentamidine and to comment on the inaccurate data which supporters of the Fisons Corporation ("Fisons") have apparently presented to you and your staff concerning their method of administering aerosol pentamidine. I have been involved in the research and development of pentamidine for 6 years. I was one of the principal investigators in the pentamidine clinical trial that resulted in FDA approval of aerosolized pentamidine for prophylaxis against Pneumocystis carinii pneumonia ("PCP") on June 15, 1989. In addition, I have lectured on the research and development of aerosolized pentamidine to diverse audiences in both the United States and Canada.

I have had an opportunity to review two charts (copies enclosed) apparently provided by supporters of Fisons to your staff, the presentation by Fisons to the FDA Antiviral Drug Products Advisory Committee on May 1, 1989, the written submission by Fisons to the Public Health Service task force, and presentations of Fisons data at scientific meetings and in the medical literature.

From this review, I have discovered mischaracterizations in the charts presented to you that misrepresent the Fisons dosage regimen and its nebulizer (FISONeb) as therapeutically superior to the dosage regimen approved for Lyphomed which uses the Marquest nebulizer (Respirgard II). In reality, the Fisons regimen and nebulizer are not therapeutically superior to the Lyphomed regimen and nebulizer in any way and are in fact very unlikely to be as effective in preventing PCP. As a clinical investigator who is very close to the development of pentamidine and very interested in the treatment of AIDS patients, I felt an obligation to write to you to correct the record with respect to the Fisons data.

All of the Fisons and Lyphomed pentamidine data were reviewed and evaluated in the spring of 1989 by a select committee of the U.S. Public Health Service convened by Dr. Anthony Fauci of NIH and chaired by Dr. Henry Masur of NIH. That committee included clinical investigators involved in the Fisons trials, experts from the FDA, and other experts in the field. In a report published in the June 16, 1989 Morbidity and Mortality Weekly Report (copy enclosed), this committee concluded that the only pentamidine regimen with established efficacy is 300 mg every 4 weeks delivered by the Respirgard II (i.e., the Lyphomed regimen). In a consensus statement by the committee, undisputed by the Fisons clinical investigators, it was stated that there was insufficient data to recommend any other nebulizer regimen. No new clinical data supporting the Fisons regimen have been presented to change that evaluation since the committee's report was issued.

Fisons has presented no data from human beings to establish the efficiency of pentamidine delivery to the lungs by the FISONeb nebulizer. The data Fisons has presented to you on the deposition of pentamidine in the lungs through the FISONeb is based on _in vitro_ laboratory tests of their nebulizer. Such _in vitro_ data cannot, of course, be extrapolated legitimately to human beings. Fisons simply does not know whether the FISONeb produces acceptable levels of pentamidine in the lungs of AIDS patients. In contrast, the nebulizer used with the Lyphomed product has been tested in a human clinical trial which measured the levels of pentamidine in the lung after aerosolization by the Respirgard II. In this clinical study, the Respirgard II nebulizer produced extremely high pentamidine levels in the alveoli (air sacs within the lung) when measured directly. Montgomery, A.B. _et al_., "Selective Delivery of Pentamidine to the Lung by Aerosol", _Am_. _Rev_. _Respir_. _Dis_., Vol. 137, pp. 477-478 (1988) (copy enclosed).

The Fisons nebulizer produces a large particle size which is more likely to irritate the respiratory passages (leading to bronchospasm) and thereby to reduce the amount of pentamidine available to the lung tissue. Although Fisons has presented data to you that the MMAD (mass median aerodynamic diameter) (i.e., the size relative to which half of the particles are larger and half are smaller) of its nebulizer particles ranges from 2.3 to 4.6 microns, in reality the particle size MMAD for the FISONeb nebulizer, as reported in several articles from the medical literature and in the Fisons package insert, is in the range of 4.5 to 5.0 microns.[1] In contrast, the Respirgard II has an MMAD of 1 to 1.5 microns. Montgomery, A.B. _et al_., "Selective Delivery of Pentamidine to the Lung by Aerosol", _Am_. _Rev_. _Respir_. _Dis_., Vol. 137, pp. 477-478 (1988) The smaller size of the particles associated with aerosolization of the Lyphomed pentamidine product is important because it permits more drug to reach the site of action in the lung without irritation to the lung tissue.[2]

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[1] For example, see Corkery, K.J., Luce, J.M., and Montgomery, A.B., "Aerosolized Pentamidine for Treatment and Prophylaxis of _Pneumocystis carinii_ Pneumonia: An Update", _Respiratory Care_, Vol. 33, No. 8, pp. 676-685 (August 1988) and Smith, D. _et al_., "Comparison of Nebulizer Efficiency for Aerosolizing Pentamidine", Abstract T.B.P. 64, V International Conference on AIDS, Montreal, Canada, June 4-9, 1989 (copies enclosed). There is one article in the medical literature which suggests the MMAD of the FISONeb to be 2.5 microns. Smaldone, G.C. _et al_., "Characteristics of Nebulizers Used in the Treatment of AIDS-Related Pneumocystis Carinii Pneumonia," _J. Aerosol Medicine_, Vol. 1, No. 2, pp. 113-26, (1988) (copy enclosed). This assessment of particle size has been widely recognized as flawed because of an error in the technique of measurement used by Smaldone. In brief, the measuring device used by Smaldone eliminated larger particles from the measurement, as a result of a design defect, and left only the smaller size particles to be measured. This skewed the MMAD measurement to a low value, one which has never been replicated by other investigators who have measured the particle size (MMAD) of the FISONeb. In fact, using a standard method, in the same paper, Smaldone presented a particle size measurement (MMAD) of greater than 5.0 microns for the FISONeb.

[2] It should also be noted that the pentamidine drug particles become larger once they reach the lung tissue because pentamidine molecules expand in a humid environment such as the lung (termed a "hygroscopic" effect). The FISONeb particles, which are already approximately four times larger than the Respirgard II particles, will thus become even larger in the lung, resulting in additional airway irritation and reduced effectiveness.

The chart submitted to your staff on nebulizer efficiency is inaccurate. Data from the Lyphomed NDA for aerosolized pentamidine showed the Respirgard II nebulizer to have an efficiency of 10-11%, not 3% as suggested by Fisons. The Smaldone article, cited above in footnote 1, purports to establish an efficiency for the FISONeb nebulizer of 16% and an efficiency for the Respirgard II of 4.6%. These efficiency figures in the Smaldone article are not accurate as a direct comparison because of a failure to consider and correct for the time of administration which differs between the two nebulizers. The FISONeb delivers all its drug product in a period of 20 minutes whereas the Respirgard II delivers its complete dosage in approximately 40 minutes[3]. Smaldone measured the efficiency of the Respirgard II in 20 minutes as 4.6%; in 40 minutes, that efficiency would be doubled to 9.2%. And, although the FISONeb has an efficiency of 16% in the 20 minutes that it takes to finish its delivery, one can see from the graph submitted by Fisons (enclosure) that at least half of the particles generated by the FISONeb do not fall in the range of alveolar deposition. Correcting for this reduces the FISONeb efficiency by half, to a figure of 8%. In contrast, the Respirgard II, by virtue of its superior design, produces almost all of its particles in the range of alveolar deposition so the 9.2% efficiency figure need not be corrected in this way. In summary, when one compares the efficiency of the Respirgard II with the FISONeb, correcting for the time it takes for each to deliver its full dose of drug and the amount that reaches the lung, FISONeb has an efficiency of approximately 8% and Respirgard II an efficiency of approximately 9.2%.

A nebulizer that delivers its product in a lesser amount of time does not necessarily result in a clinical advantage. What counts is the amount of drug that reaches the site of action. More drug reaches the lung with the Respirgard II in 40 minutes, as a result of its smaller particle size, than the amount that reaches the lung in 20 minutes with the FISONeb. In fact, a longer administration time for nebulized particles into the lung may be preferable because it results in less irritation as the lung tissue has a longer period of time to react to the bombardment of nebulized particles.

Ultimately, this type of comparison of nebulizer efficiency only provides a theoretical basis for predicting what might occur. Only clinical trials, in which human beings utilize the drug, can provide hard evidence of effectiveness. Those trials have, of course, been done on the Lyphomed regimen and have shown its effectiveness.

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[3] The period of approximately 40 minutes for the nebulizer chamber of the Respirgard II to be emptied was determined in clinical trial use for the prophylaxis of patients and is referenced in the approved labeling for Lyphomed's product NebuPent. Smaldone's suggestion that the use of the Respirgard II is limited to 20 minutes by patient fatigue is apparently based on its use by patients in a study for the treatment of acute pneumonia, patients who were weakened by the presence of an acute respiratory disease. Accordingly, to validly compare the efficiency of nebulizer emptying between the Respirgard II and FISONeb, the standard emptying times -- 40 minutes for the Respirgard II and 20 minutes for the FISONeb -- must be used.

A report in The Pink Sheet (F-D-C Reports, September 25, 1989), which discussed the Fisons dose-ranging study at Northwestern University, stated that "[e]stimates for 24-week PCP-free survival were 100% in the 60 mg group, 90% in the 120 mg group, and 79% in the 5 mg group." While the fact that the 120 mg group (higher dose regimen) seems to have less effectiveness than the 60 mg group (lower dose regimen) is probably attributable to the fact that a study of such a short duration could not provide meaningful results (see discussion below), another real possibility is that the ultrasonic nebulizer produces too much bronchospasm at the higher dose to be effective. Bronchospasm actually interferes with delivery of the drug to the air sacs of the lung.

Ultimately, all of the reported Fisons data from controlled trials suffer from the same fatal deficiency - its studies as reported were too short, with no results reported after six months. Lyphomed also saw encouraging trends at lower doses in the first six months of its own clinical trials. In fact, in an analysis of our six-month data, we drew the erroneous conclusion that 150 mg twice a month would be superior to 300 mg once a month. Ultimately, by continuing the study over an 18-month period, we learned that the 300 mg once a month dose is superior. By continuing the study through a period of 18 months, Lyphomed learned that most of the pneumonia relapses suffered by these patients in fact occurred after the point at which Fisons terminated its study -- i.e., between the 6 to 12 month periods. Fisons has not reported controlled studies past the six-month period and therefore the Fisons data are likely to be artificially positive and clinically meaningless.

Any claim that the Fisons regimen and nebulizer is equivalent to the FDA-approved regimen using the Respirgard II nebulizer would have to be substantiated by head-to-head clinical trials (i.e., clinical trials in which the two regimens are compared under equivalent circumstances.). If, however, one seeks to compare existing clinical data, that comparison does not support the Fisons claim. One could look at participants in Lyphomed's trial who would have met the criteria for inclusion in the Fisons protocol to obtain some information about the difference in effectiveness of the two regimens. At the end of six months (the end of the Fisons controlled trial), the equivalent participants in the Lyphomed trial who received 300 mg once per month had approximately one half as many PCP relapses as those in the Fisons trial who received 60 mg twice a month. Fisons' open trial also shows a much higher one year attack rate than the Lyphomed study or its open trials. Thus, the evidence that Fisons provides suggests that Fisons' dose is too low or that its nebulizer has problems delivering drug to the appropriate areas of the lung.

I am concerned that Fisons may try to suggest that its regimen would be cheaper by assuming unsupervised home use of its nebulizer. There are significant health problems associated with unsupervised home use of a nebulizer for PCP prophylaxis. Aerosolized pentamidine treatments have shown the need for scrupulous infection control to prevent transmission of other pulmonary infections. The Fisons nebulizer lacks disposable components or an expiratory filter, the presence of which helps to prevent the risk of transmission of infection and environmental (second hand) exposure to exhaled pentamidine. In any case, supervision would be necessary to prevent transmission of tuberculosis and other infections to household members. Patients are not likely to buy devices for one use only and, given the major expense of a single Fisons nebulizer ($350 each compared to $6 for the disposable Respirgard II), AIDS patients will undoubtedly share these Fisons nebulizers -- a grim prospect considering the likelihood of transmission of respiratory infections from person to person from such sharing.

Further, since aerosol treatments are prolonged and time consuming, it is unlikely that compliance with treatment will be as good with any unsupervised home treatment. Because the Fisons clinical trials are supervised in a hospital or clinic setting, it is not clear that their results would be generalizable to treatments performed at home by patients who are unsupervised. In fact, many AIDS patients are not physically able to coordinate breathing with triggering the nebulizer, as required by the FISONeb nebulizer.

I am quite distressed that the Fisons data, as presented to you, falsely imply that the Fisons pentamidine regimen and nebulizer could be considered as equivalent or superior in efficacy to the Lyphomed regimen which has been proven safe and effective in clinical trials. The simple truth, as demonstrated by an objective look at the data which exist to date, is that the Fisons regimen and nebulizer are not equivalent or superior to the currently approved pentamidine formulation. The lives of AIDS patients are at stake, compelling us to take a fair look at the available data. I hope that the discussion above will assist you in that process.

Sincerely,

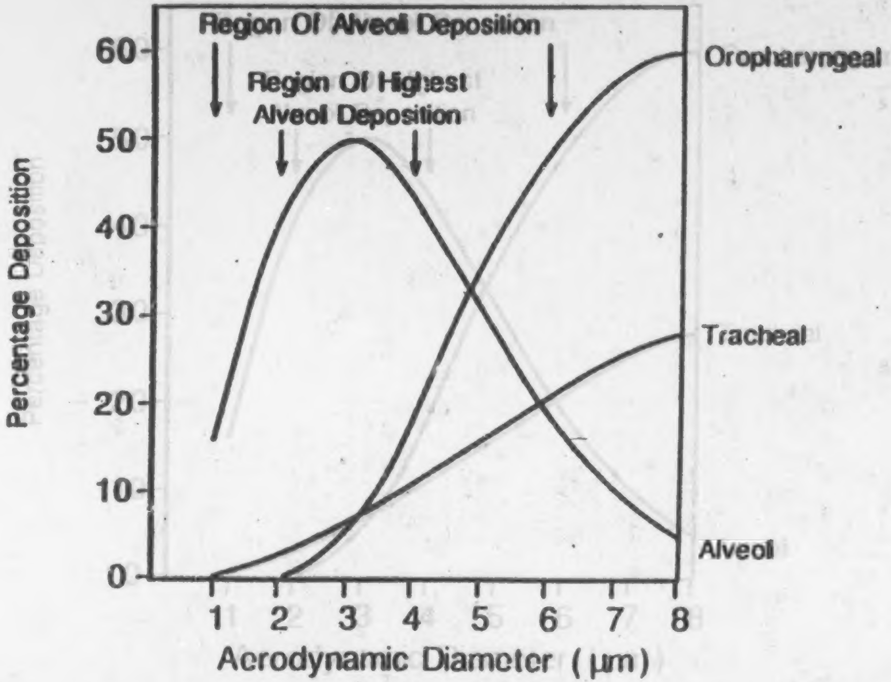
Bruce Montgomery M.D.

Bruce Montgomery, M.D.

cc: Mr. James S. Benson
Acting Commissioner
Food and Drug Administration

DEPOSITION EFFICIENCY VERSUS AERODYNAMIC DIAMETER AFTER STAHLHOREN

(Steady breathing, inhaled volume 1.5 litres,
breathing frequency 15 mm^{-1})



PNEUMOPENT

NEBULIZER - FEATURES

FISONeb	MARQUEST
ULTRASONIC	JET
MMAD 2.3 - 4.6u	MMAD 0.3 - 1.6u
High Efficiency (16%)	Low Efficiency (3%)
Fast 4-5 min Continuous 15-20 min normal use	Slow 30-45 min Continuous
Coordinated with Inspiration	Continuous
No Filter	Filter

Lyphomed

Brian Tambi
Senior Vice President & General Manager
Ethical Pharmaceutical Division

January 17, 1990

Mr. James S. Benson
Acting Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD

Dear Mr. Benson:

We understand that the Food and Drug Administration has been asked by Senator Pryor to provide analysis and advice regarding a legislative proposal to change the Orphan Drug Act. The change in question would be designed specifically to benefit a British pharmaceutical company, the Fisons Corporation, by authorizing FDA to approve a Fisons NDA for pentamidine, despite the exclusivity granted to Lyphomed for that drug. This request is based on the Senator's understanding that Fisons has allegedly developed a "clearly superior technology," that would allow pentamidine to be used effectively in prophylaxis of Pneumocystis carinii pneumonia ("PCP") at lower doses and thus lower cost than the dosage and nebulizer currently approved by FDA.

Our submission herein will establish that the premise for Senator Pryor's proposal is unsupported by factual data and without clinical or scientific merit. Fisons' proposed prophylaxis regimen has not been shown to be therapeutically equivalent, much less superior, to that covered by Lyphomed's approved new drug application. Moreover, the alleged reduction of patient cost of the Fisons' drug and Fisons' nebulizer is without basis as well.

A second argument by Senator Pryor for the proposed amendment to the statute -- that Lyphomed has abused the Orphan Drug Act -- is simply false. Finally, any change to decrease or dilute marketing exclusivity under the Orphan Drug Act would be, we believe, poor public policy. Any action to alter the law to favor individual companies, and in particular a foreign company such as Fisons, would be detrimental to the entire United States system of intellectual property rights and will have serious implications throughout the whole U.S. pharmaceutical industry. In this letter we address each of these points.

Safety and Effectiveness

We have reviewed the Fisons claims with experts familiar with pentamidine prophylaxis who were present at the Fisons' presentation at the FDA Antiviral Drug Products Advisory Committee meeting on May 1, 1989. These experts have also reviewed Fisons' written submission to the Public Health Service Task Force. We feel compelled to share with you the following observations by our expert consultants concerning the Fisons data.

Fisons relies, in part, on a placebo-controlled trial. In general, a placebo trial can quickly establish whether an experimental drug has activity, but unless there is complete suppression at a low, well tolerated dose, it does not answer the question of optimal dose. Indeed, Fisons has recognized and acknowledged this by conducting a dose ranging study concurrently (the results of which will be discussed in a following section). Experts whom we have consulted believe there are several shortcomings with data from even a dramatic placebo trial, shortcomings that are evident in Fisons' data:

a. If the drug is very active, then a placebo trial will be of very short duration, which does not allow long-term assessment of continued efficacy and safety. Both in natural history studies before prophylaxis and in our own trials, the majority of PCP events seen do not occur until after the first six months of prophylactic therapy. Indeed, at a comparable period (at six months follow-up) in our trial we could barely discern whether the 30 mg dose was as effective as the 300 mg dose. In fact, based on those early trends, the incorrect extrapolation was made by us that 150 mg bi-weekly would be the optimal dose, in recommendations to the NIH about study designs.

   After 6 months prophylaxis, however, dose separation started to show and long-term (18 months) follow-up clearly established that 300 mg every four weeks was the optimal dosage regimen. The Lyphomed NDA submission in November 1988 was based on a 12-month follow-up analysis of the dose-response prophylaxis study. The FDA required from Lyphomed an 18-month follow-up analysis to ensure that the superiority of 300 mg dose was established with a full year of data following the first appearance of a dose response. There is no public evidence that Fisons has 18-months of patient follow-up in any study.

b. If the drug is very active, even small doses not effective in the long run will be better than the placebo in the short-term. This is the erroneous trend that Fisons' 6 month study showed.

c. The strategy for testing drugs for acute treatment is very different from that for testing for prophylaxis. For acute treatment of a life-threatening condition, the maximally tolerated dose is given, and if that is ineffective it can be abandoned. If it works, then follow-up studies can elicit whether lower doses are as effective. With prophylaxis, however, there is no logic at all to giving a maximal dose (in this case that would be daily IV pentamidine dose of 4 mg/kg). Only a dose response study can show the optimal dose for prophylactic therapy.

Although it is difficult to compare Fisons' dose-response study to Lyphomed's, some scenarios can be offered to provide perspective. If one takes a cohort of Lyphomed study participants who would have been eligible for Fisons' study, and compares our results to those of Fisons, the Fisons results at six months show a two fold greater PCP rate for their 120 mg per month in two doses than that observed in the group receiving our 300 mg single dose per month. The Fisons' open trials also shows a much higher one year attack rate than our pivotal study or our open trials. Thus, the evidence that Fisons provides suggests that its dose is too low and consequently less effective than Lyphomed's dosage regimen and/or that its nebulizer has problems delivering drug to the appropriate area of the lung.

These data lead us to conclude that Fisons has not shown equivalency, let alone the company's claimed "superiority," in terms of relative efficacy and safety of aerosolized pentamidine delivered via Fisons' nebulizer as compared to Lyphomed's FDA-approved dose and device.

We note that our view on this issue was shared by the panel of experts convened by the National Institutes of Health to draft guidelines for PCP prophylaxis. Incidentally, that panel included Dr. Donald Armstrong, a Fisons collaborator and principal proponent of the Fisons technology. The Fisons data were presented to the panel for its consideration. The panel concluded that the 300 mg dose of pentamidine, administered every 4 weeks using the Respirgard II jet nebulizer, which was not yet approved by the FDA as of that date, should be used for prophylaxis. As you know, at the time of that analysis, Fisons had stopped its trials and the results were known to the panel. The panel concluded that: "Because other doses and aerosol delivery systems [*i.e.*, other than those developed by Lyphomed] have not been adequately studied and analyzed, no recommendations regarding such systems can be made." MMWR, Vol. 38, No. S-5, pg. 6.

It is, we believe, particularly noteworthy that in Europe, where Fisons is based, where its nebulizer is freely available, and where there is no restriction on its use, Europe's standard medical practice is the use of the 300 mg pentamidine dose and the Respirgard II nebulizer. Thus, with their patients' welfare at stake, European physicians have made the independent determination that Fisons' dose and nebulizer have not been shown to be equivalent in efficacy to that developed by Lyphomed.

Our experts in fact think, based on their own practice and understanding of the drug and its aerosol administration, that Fisons' regimen and nebulizer is considerably less effective.

A major problem lies with Fisons' nebulizer. A particular difficulty with aerosol administration of pentamidine is that pentamidine is an airway irritant. If a medium sized particle nebulizer like the FISONeb is used, because of the larger size of the aerosol particles a substantial amount of drug deposits in the upper airways, resulting in serious airway irritation causing cough or bronchospasm. Therefore, the higher the dose used with a medium sized particle nebulizer (such as Fisons' nebulizer), the greater the chance of serious side effects. The bronchospasm actually interferes with the delivery of drug to the alveoli resulting in ineffective treatment. Thus, a trade press report stated that, in the Fisons' dose-ranging study at the Northwestern University site "estimates for 24-week PCP-free survival were 100% in the 60 mg group, 90% in the 120 mg group, and 79% in the 5 mg group." It is likely this association of higher dose with lower efficacy is because the study was too short in duration to obtain accurate estimates of efficacy. Another and also plausible possibility is that Fisons' ultrasonic nebulizer produces too much bronchospasm at the higher dose to sufficiently deliver drug to the alveoli and thus was not effective in some patients.

We also invite your attention to the fact that, unlike Lyphomed, Fisons has, to our knowledge, never seriously investigated the use of its nebulizer in treatment (as opposed to prophylaxis) of PCP. That is probably fortunate. Some experts believe that the use of a nebulizer producing larger particles in the treatment context could be life threatening as it might result in ineffective treatment.

The best clinical results, both in treatment and in prophylaxis, to date have been reported with a small particle nebulizer such as the Respirgard II used by Lyphomed (manufactured and sold by Marquest). Thus, based on clinical evidence in humans in both treatment and prophylaxis, a small particle nebulizer (that minimizes bronchospasm while maximizing delivery to the alveoli where PCP is found) is the optimal device. Montgomery AB: "Pneumocystis carinii Pneumonia in Patients With the Acquired Immunodeficiency Syndrome: Pathophysiology, Therapy, and Prevention." Seminars in Respiratory Infections. 1989: (4); 102-110 (copy provided); Corkery KJ, Lucy JM, and Montgomery AB: "Aerosolized Pentamidine for Treatment and Prophylaxis of Pneumocystis carinii Pneumonia: an Update." Respiratory Care. 1988: (33); 676-685 (copy provided).

The current state of the art in small particle nebulizers is the Respirgard II, which is why the Respirgard II was used in all Lyphomed trials after careful evaluation. The Respirgard II has proved to be very successful over the past three years of widespread prophylactic use throughout the United States.

Ultimately, in the absence of a head-to-head trial, the question whether Fisons' dose and nebulizer are equivalent to those shown to be effective in Lyphomed's trials and in widespread practice will never be conclusively answered. Certainly, in light of the evidence to the contrary, it would be very imprudent to assume equivalence.

Cost of Therapy

Fisons' claim to lower cost to the patient/user has no basis in fact. As we will demonstrate, an analysis of the cost of administration of pentamidine according to Fisons' regimen shows that Fisons' regimen will ultimately cost more than the cost of the currently approved Lyphomed regimen. Typically, the cost of drug has been a relatively minor component of the total cost of administration. If one compares the cost of Lyphomed's once monthly therapy with that of Fisons' low-dose, bi-monthly administration, the benefit of reduced drug cost is more than offset by increases in labor and equipment costs which directly increases the cost to the patient. It is important to note that, unlike Lyphomed, Fisons owns and markets the nebulizer (FISONeb) used in their regimen. Thus, their claim is an illusory cost reduction that trades off lower drug price with a high nebulizer price. Fisons strategy is to make money on its nebulizer.

The costs comparisons we provide are based on the following facts and assumption:

- Lyphomed's regimen uses the Respirgard II nebulizer, which costs $6 and is disposable.
- In hospital clinics, the Respirgard II is attached to wall air outlets. Thus, the air supply involves no additional costs.
- In physician offices and home care settings the Respirgard II requires a compressor, which can be reused by many patients. We assume for purposes of this cost comparison a very conservative estimate of five patients per month per physician office.
- Compressor prices range from $200 for a unit that may be attached to one nebulizer at a time to $450 for a unit to be used by four patients at once. Thus, we assume a $240 compressor cost.
- Fisons' regimen used the FISONeb nebulizer, which costs $350.
- The FISONeb is reusable, but it would be unsafe, without extraordinary precautions, to use it on more than one HIV positive patient because of the risk of transmission of pulmonary infections. We assume that FDA would not allow sharing of a FISONeb by multiple HIV positive patients.
- For comparative purposes, we amortize both the compressor and the FISONeb over 12 months.
- We assume, as does Senator Pryor, that if allowed to market pentamidine Fisons would sell the drug at $20 for a 60 mg dose (i.e., the same cost per mg as Lyphomed's 300 mg dose).
- Finally, as discussed in the preceding section on efficacy, if the Fisons 60 mg dose is not as effective as the approved Lyphomed regimen, the cost of hospitalizing a patient with acute PCP ranges from $12,000 to more than $30,000.

In considering the comparisons, the following should be kept in mind:

- The administration costs used are very conservative.
    - We compute a hospital clinic cost for NebuPent administration of $160.45. Actual clinic costs from San Francisco range from $175 to $280 per administration, which would be double for the Fisons regimen of twice monthly administration.
    - Home care may cost much more than the estimates we use.
- Doubling the number of administrations (required by the Fisons' regimen) would:
    - Increase the burden on HIV positive individuals in scheduling appointments, thus decreasing compliance.
    - Overload public and private clinics facing increasing demands for PCP prophylaxis.

With that introduction, the following calculations demonstrate that the Fisons claim to being more economical is simply baseless. In fact, Fisons regimen is more costly particularly in the home care setting:

MONTHLY COST OF PENTAMIDINE PROPHYLAXIS

HOSPITAL CLINIC

	Lyphomed[1] Regimen 300 mg. q 4 weeks	Fisons[2] Regimen 60 mg. q 2 weeks
DRUG:	$99.45	$20.00 x 2 = $40.00
EQUIPMENT:		
Nebulizer -	$ 6.00	$29.00 - $86.00[3]
Compressor -	N/A	N/A
LABOR:		
R.T.T. Time	$50 hr x 1 = $50	$50 hr x 2 = $100
Rx Fee	$ 5	$ 5 x 2 = $ 10
	$160.45	$179.00 - $236.00

DOCTOR'S CLINIC

	Lyphomed[1] Regimen 300 mg q 4 weeks	Fisons[2] Regimen 60 mg q 2 weeks
DRUG:	$99.45	$20.00 x 2 = $40.00
EQUIPMENT:		
Nebulizer -	$ 6.00	$29.00 - $86.00[3]
Compressor -	$ 4.00[4]	N/A
LABOR:		
M.D. fees -	$50	$50 hr x 2 = $100
Rx Fee	$ 5	$ 5 x 2 = $ 10
	$164.45	$179.00 - $236.00

MONTHLY COST OF PENTAMIDINE PROPHYLAXIS

HOMECARE

	Lyphomed[1] Regimen 300 mg q 4 weeks	Fisons[2] Regimen 60 mg q 2 weeks
DRUG:	$99.45	$20.00 x 2 = $40.00
EQUIPMENT:		
Nebulizer -	$ 6.00	$29.00 - $86.00[3]
Compressor -	$20.00[5]	N/A
LABOR:	$100.00[6]	$100.00 x 2 = $200.00
	$225.45	$269.00 - $326.00

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[1] Lyphomed FDA approved dosage regimen.

[2] Fisons proposed regimen.

[3] FISONeb purchase price = $350 = $29 per month; FISONeb rental = $86.00/month.

[4] Compressor purchase price = $240 divided by 12 = $20 per month divided by 5 patients = $4 per patient per month.

[5] Annualized compressor purchase price.

[6] Average of charges (CareMark, H.N.S., I.C.S. Homecare Companies). Labor charges by homecare companies vary widely. Charges for home administration of NebuPent have been reported as high as $400 per treatment in some areas. Thus, Fisons biweekly regimen will be prohibitive for home care in some areas.

The solution to the problem of administration costs cannot, moreover, be solved by administration of pentamidine through unsupervised use of the Fisons device. Aerosolized pentamidine treatments have underscored the need for scrupulous infection control to prevent transmission of other pulmonary infections. Fisons' device lacks disposable components to prevent transmission of TB and other infections (such as pseudomonas infections) to household members or patients themselves. Use of the Fisons' device without supervision would only increase the risk of such transmission. It is, moreover, questionable whether unsupervised patients would buy Fisons' device for single use: given the expense of the unit it is predictable that many would share these devices, further increasing the potential for spread of other communicable diseases. Since aerosol treatments are also very time consuming, unpleasant and disruptive to normal routine, it is unlikely that compliance with treatment would be as good with unsupervised home treatment. Because Fisons' trials were center supervised, it is not at all clear that their results would be generalizable to home treatment.

Lyphomed's Development of Pentamidine

Senator Pryor's letter suggests that Lyphomed has abused the Orphan Drug Act by its pricing of pentamidine. That assertion is unfair and may reflect an incomplete understanding of the historical facts concerning the development of pentamidine. Lyphomed has taken its responsibilities to develop pentamidine under the Orphan Drug Act very seriously.

As the FDA is well aware, injectable pentamidine has serious toxicity. If used inappropriately, patients can be harmed, or the drug can be ineffective in the treatment of a fatal disease. In 1984, when Lyphomed was asked to market this drug, many physicians were just beginning to learn to manage AIDS cases. If those physicians were not properly informed about pentamidine's profile and its correct medical use, the drug's life saving capabilities would be lost to those physicians' patients.

It thus became apparent that Lyphomed would have to develop a physician marketing and educational capability. Lyphomed, at that point, was of course faced with a choice. It could have turned away from its responsibility to educate the medical community about pentamidine and kept its price as originally set. Patients since saved by pentamidine would have died if Lyphomed had chosen that course. But Lyphomed would not have been criticized for its pricing. Instead, Lyphomed decided that the responsible course of action was to develop a physician education capability. Thus, the price of pentamidine had to be raised to pay for that program.[7]

Also in 1984, researchers approached Lyphomed seeking support for potentially important research with the drug. If the drug could be administered by the aerosol route, they theorized, the serious side effects might be avoided and use for prophylaxis could be considered. It soon became apparent that the costs of testing aerosol inhalation in both prophylaxis and acute treatment would be very great.

Again, Lyphomed could have turned its back on this research. Like the manufacturers of trimethoprim-sulfamethoxazole, it could have declined to provide more than token support for research concerning its drug. Had it done so, Lyphomed could have kept the price of the drug lower and avoided much of the present controversy. Lyphomed could not, however, refuse to support potentially life-saving research. Consequently, the price was raised in increments to pay for what turned out to be, ultimately, a very expensive research program. The last price rise was in August of 1987. The price has not been increased since that time, despite escalating costs of current and future research.

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[7] In an April 1988 hearing that addressed this issue, Congressman Weiss suggested that Lyphomed might have accomplished this purpose by licensing the drug out to another company with an existing physician education capability. But no other company was interested in pentamidine at that time. Further, even if Lyphomed had licensed the drug to a major company, there would be no guarantee that the price would not have risen, as Congressman Weiss agreed. Certainly no company would use a detail force without recovering the cost. Thus, a price increase would be inevitable.

Then, in October 1987, the day Lyphomed revealed its research results as of that date in a Lyphomed-sponsored national seminar chaired by Dr. Donald Armstrong at the Memorial Sloan Kettering Cancer Center, Fisons announced in London, England to Lyphomed's shock and surprise, that Dr. Armstrong was working with Fisons.

This British company was now prepared to reap the rewards of early research supported by Lyphomed. Lyphomed was subsequently informed that Dr. Armstrong had entered into the agreement with Fisons as far back as June 1987, but did not reveal this association until after the Lyphomed research seminar in October 1987, which he chaired. To our knowledge, Fisons had conducted no research on PCP prophylaxis prior to its agreement with Memorial Sloan Kettering in mid-1987.

FDA granted Fisons Orphan Drug Act designation. That meant that, if Fisons had been able to show that its dosage and nebulizer worked before Lyphomed's own NDA for prophylaxis was approved, Lyphomed would have been barred from the market.

Lyphomed's investment in aerosol pentamidine research was now very much a business risk. Lyphomed shouldered that risk because of its concern for the people that would be helped by the research and because of the return on investment guaranteed by the Orphan Drug Act if Lyphomed succeeded. It is, of course, that guarantee that some are apparently now considering abridging.

In summary, Lyphomed commenced its support of development of pentamidine for PCP prophylaxis as far back as 1984 with the initial funding of preclinical research by Drs. Montgomery and Debs. Throughout 1985-1988 and continuing into 1989, Lyphomed has provided a stream of funds to other investigators, in addition to the continued support of Drs. Montgomery and Debs. Lyphomed could not have done this without the exclusivity provided by the Orphan Drug Act. The funds attributable to that exclusivity have been used to support both PCP prophylaxis and treatment trials with the aerosol formulation, as well as the technological development of new delivery systems, safer and more effective pentamidine analogues, and improved drug formulations. (As to acute treatment, Lyphomed has just completed the largest double-blind, randomized well-controlled multi-center trial for acute treatment of PCP performed to date, utilizing the aerosol delivery system. To our knowledge, no other company or organization is investigating treatment of PCP with aerosol pentamidine.)

The entire pentamidine research and development program is continuing. As you know, additional research to be funded by Lyphomed includes post-marketing studies required by the FDA such as additional large-scale primary and secondary prophylaxis trials, long-term animal aerosol toxicity studies, animal teratology studies, two-year carcinogenicity studies, and other studies.

The expenses to date for all pentamidine studies are estimated at $23 million. The FDA-required post-marketing studies are preliminarily estimated to cost at least an additional $15-$20 million over a period of at least 3 years. Also, the company is supporting a pediatric trial of inhaled pentamidine and supporting 51% of a number of NIH aerosol trials in AIDS patients.

Lyphomed is, in addition, supporting research into improved delivery systems for pentamidine and pentamidine analogues that may be essential if PCP should become resistant to pentamidine in its present form. One variant of pentamidine currently being researched may be amenable to an oral dosage form -- allowing pentamidine prophylaxis for children who cannot use the nebulizer and decreasing administration costs significantly. This research is all extremely expensive, and Lyphomed is the only company engaged in such research and development.

The total cost to be borne by Lyphomed is enormous and will be ongoing over the next 3-5 years. This expense extends beyond the period of market protection provided by the Orphan Drug Act, which for all practical purposes expires in October 1991 -- i.e., in less than two years. Although Lyphomed has seven years of exclusivity for aerosol prophylaxis (June 15, 1989 through June 15, 1996), once injectable pentamidine becomes available for generic marketing in October 1991, the company in effect loses nearly five years of this orphan drug "exclusivity."

Effect of Orphan Drug Act Amendment on Orphan Drug Development

The amendment to the Orphan Drug Act suggested in Senator Pryor's letter is represented to be no more than a "technical change" in the statute that would nevertheless preserve the incentives of the statute. As we believe you will agree, the signal that would be sent by adoption of such an amendment would have far-reaching effects on decisions by pharmaceutical companies considering investment in orphan drug research. If the statute's grant of exclusivity can be abrogated simply because a second company's nebulizer allegedly provides cheaper treatment and the benefits of exclusivity can be withdrawn, exclusivity will be meaningless, especially when it is needed, i.e., whenever more than one company is "racing" for approval. If exclusivity is to be abridged whenever a second company can claim that it "has developed a clearly superior technology," even though it has not performed head-to-head testing to show equivalence, much less superiority, the risk would be ever-present that exclusivity, once earned, would be taken away by subsequent Congressional action.

The National Commission on Orphan Diseases reported sponsors of orphan drugs as concluding that "if they had known what was in store for them, they would probably not have undertaken the sponsorship of their respective orphan drugs," NCRD Report, page 99. One thing that is surely in store for any company that produces an important orphan drug is a lobbying effort by a competitor to change the law so as to take away the drug's exclusivity. The arguments made for change are plainly self-serving -- the loser in the race for approval lost its investment and, if allowed onto the market, would offer the drug at a lower price.

The National Commission on Orphan Diseases ultimately recommended that the incentives for development of new orphan products be increased, not decreased or made more uncertain. Id. at 100. The Commission based that recommendation in part on a concern that the "incentives offered by the Orphan Drug Act are not compelling enough to warrant the diversion of corporate resources towards discovery and development of products for the rare diseases." Id. at 99. Those incentives would, of course, be seriously undercut if the exclusivity the statute now offers could be devalued by the type of "technical change" which Senator Pryor has asked FDA's advice on.

The development of aerosol pentamidine for PCP prophylaxis is truly an Orphan Drug Act success story. It is literally true that lives are being extended and saved by pentamidine prophylaxis today because of the efforts not only of Lyphomed but also, and especially, of those legislators with the wisdom and foresight to pass an Orphan Drug Act that provided meaningful market protection for orphan drugs.

We believe, frankly, that Lyphomed deserves credit for this achievement. The record demonstrates that Lyphomed has done an outstanding job in fulfilling its responsibilities, as a holder of Orphan Drug Act exclusivity, to develop pentamidine to its full potential. We hope that you will agree that the circumstances concerning this drug do not warrant an amendment of the statute that would adversely affect both Lyphomed, and by making Orphan Drug Act incentives more uncertain, the future of all orphan drug development.

Conclusion

Senator Pryor's letter to the FDA reflects some one-sided and non-factual assertions by representatives of Fisons Corporation. We are encouraged that the Senator has sought further information from the Agency before proceeding with a proposed amendment that would be, we believe, unjustified, not in the public interest and particularly against the best interest of people with AIDS. We trust that you will consider each of these points as you prepare your response to Senator Pryor.

Sincerely,

Brian Tambi

Brian Tambi

Enclosures

cc: Senator David Pryor

The Lancet
November 25, 1989

Letter to the Editor

AEROSOLISED PENTAMIDINE

SIR,—Like Dr McDiarmid and Dr Jacobson-Kram (Oct 7, p 863) we have been concerned with the potential hazards to public health associated with aerosolised pentamidine. Aerosolised pentamidine should be administered by suitable apparatus. Some nebulisers (eg, 'Respirgard II' and 'Samsonic') are supplied with suitable filters to prevent escape of aerosol. For others (eg, 'System 22 Mizer') filters can be obtained separately, but systems such as 'Pulmosonic', 'Portasonic', and 'Fisoneb' will not take commercially available filters, and unless customised modifications are made escape of aerosol is inevitable.

We have measured pentamidine contamination of the environment when these nebulisers are used. A filter was placed over the exhalation port so that deposition of aerosol in this filter represents aerosol that would have escaped. When ^{99m}Tc-labelled human serum albumin is added to the pentamidine solution in the nebuliser, activity correlates well with pentamidine concentration in particles of different sizes and nebuliser output is not affected.[1] Atmospheric contamination by pentamidine can be estimated by measuring the activity retained in the filter at the end of the treatment. For a nebuliser dose of 300 mg, we found losses to the atmosphere of 21·3 (SEM 16·3) mg for pulmosonic, 15·5 (5·9) mg for portasonic, and 26·3 (9·3) mg for fisoneb systems.

Although these values represent a small proportion of the total nebuliser dose there is clearly a risk of significant atmospheric contamination if groups of patients receive their therapy over a short time and in a poorly ventilated room. Physicians prescribing aerosolised pentamidine should select a nebuliser that carries the lowest risk of potential harm to their staff.

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1. O'Doherty MJ, Thomas SHL, Page C, et al. Does ^{99m}Tc human serum albumin alter the characteristics of nebulised pentamidine isethionate? Nucl Med Commun 1989; 10: 523-29.

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Guidelines for Prophylaxis Against *Pneumocystis carinii* Pneumonia for Persons Infected with Human Immunodeficiency Virus

Pneumocystis carinii *pneumonia (PCP), the most common presenting manifestation of the acquired immunodeficiency syndrome (AIDS), is a major and recurring cause of morbidity and mortality for persons infected with the human immunodeficiency virus (HIV). In recent years, important advances have been made in understanding which patient subpopulations are at highest risk for developing PCP and in the design of chemotherapeutic regimens that can reduce the frequency of this illness. Recently, a number of experts*[*] *convened by the National Institutes of Health independently reviewed data on prophylaxis against PCP among persons infected with HIV, and then provided recommendations to the U.S. Public Health Service concerning which persons should receive prophylaxis and what specific prophylactic regimens should be used. The resulting guidelines are detailed below.*

BACKGROUND

Since the early 1980's, management of PCP has become increasingly successful, and several effective chemotherapeutic regimens are available (*1*). However, such conventional therapy as trimethoprim-sulfamethoxazole or parenteral pentamidine is often complicated by adverse reactions that may require termination of the therapy (*2*), and the mortality for first episodes of PCP is still 5%-20%. Thus, prevention of PCP is a preferred alternative to treating patients for successive episodes of this disease.

Prophylaxis against PCP is categorized as primary if the goal is to prevent an initial episode for a person who has never had PCP. Prophylaxis is categorized as secondary if the goal is to prevent subsequent episodes for a person who has already had at least one episode of PCP.

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[*] Henry Masur, M.D., National Institutes of Health (Chairman); Carmen Allegra, M.D., National Cancer Institute; Donald Armstrong, M.D., Memorial Sloan-Kettering Cancer Center; Victor DeGruttola, D.Sc., Harvard University Statistical Center; Susan S. Ellenberg, Ph.D., National Institute of Allergy and Infectious Diseases; David Feigal, M.D., San Francisco General Hospital; Judith Feinberg, M.D., National Institute of Allergy and Infectious Diseases; Margaret A. Fischl, M.D., University of Miami School of Medicine; Walter T. Hughes, M.D., St. Jude Children's Research Hospital; Harold Jaffe, M.D., Centers for Disease Control; John Mills, M.D., San Francisco General Hospital; A. Bruce Montgomery, M.D., SUNY at Stony Brook; Alvaro Muñoz, Ph.D., Johns Hopkins School of Public Health; John P. Phair, M.D., Northwestern University Medical School; Frank Richards, M.D., Yale University; Fred Sattler, M.D., University of Southern California; Gerald Smaldone, M.D., Ph.D., SUNY at Stony Brook; Carol Braun Trapnell, M.D., Food and Drug Administration; Sten H. Vermund, M.D., M.Sc., National Institute of Allergy and Infectious Diseases. Consultants to the Task Force were Judith Falloon, M.D., National Institutes of Health; Michael Polis, M.D., M.P.H., National Institutes of Health; Michael Sampson, M.D., SUNY at Stony Brook.

Risk of an Initial Episode of PCP

Immunologic and clinical parameters can be helpful in determining which HIV-infected persons are at particular risk for having PCP and, therefore, which are most likely to benefit from prophylaxis against PCP. In the Multicenter AIDS Cohort Study (MACS), an ongoing prospective epidemiologic investigation of the transmission and natural history of HIV infection among homosexual men (*3*), there was a strong association ($p<0.001$) between the baseline numbers of T-helper lymphocytes (CD4+ cells) and the incidence of PCP (Table 1). Additionally, a Kaplan-Meier estimate for 323 participants whose counts of CD4+ cells were $<200/\text{mm}^3$ during the study showed that the proportions who had PCP by 6, 12, and 36 months were 13%, 24%, and 39%, respectively.

Similar results were seen when MACS data were analyzed by fraction of CD4+ cells expressed as a percentage of total lymphocytes rather than by absolute number of such cells. In a multivariate analysis of the prospective MACS data, thrush and persistent fever (temperature of >100°F) were additional independent predictors of the development of PCP among patients with CD4+ counts of $<200/\text{mm}^3$ at their most recent evaluation (Panel of experts,* Phair and Muñoz).

A retrospective study to investigate the levels of CD4+ at which adult patients develop PCP confirms the MACS data (*4*). For the 49 episodes of PCP studied, the CD4+ counts were $1\text{-}365/\text{mm}^3$ (median $26/\text{mm}^3$), and the percentage of circulating lymphocytes that were CD4+ positive was 0-25% (median 4%) within 60 days before the episode (Figure 1).

Risk of Recurrent PCP

For HIV-infected persons who have had one episode of PCP, there is a high probability that a second episode will occur if no prophylactic measures are taken. Although zidovudine will reduce the frequency of second episodes (*5*), some persons who receive zidovudine have been reported to have subsequent episodes. In an ongoing study of HIV-infected patients who have had a recently documented episode of PCP (AIDS Clinical Trial Group Study 002), zidovudine therapy was started using two different dosing regimens (*6*). The study has not yet been unblinded so that

TABLE 1. Cumulative incidence* of *Pneumocystis carinii* pneumonia (PCP) according to CD4+ count at baseline among the MACS seroprevalent cohort†

CD4+ count at baseline	N	PCP	Percentage with PCP		
			6 mo.	12 mo.	36 mo.
≤ 200	77	19	8.4	18.4	33.3
201-350	217	47	0.5	4.0	22.9
351-500	389	39	0.0	1.4	9.0
501-700	483	43	0.0	0.4	8.3
> 700	499	20	0.0	0.0	3.8

*Kaplan-Meier estimates. Both the Logrank and Wilcoxon test statistics for differences in PCP rates by CD4+ count are statistically significant ($p<.001$)

†Participants who have taken prophylactic medication have been excluded.

Source: Alvaro Muñoz, Ph.D., and John Phair, M.D., personal communication.

investigators can determine which patients received which zidovudine regimen. A preliminary analysis was done on the risk of recurrent PCP for 318 patients followed for up to 6 months and for 122 patients followed up to 12 months on zidovudine (Figure 2) (Panel of experts,* Fischl). These results indicate a need for PCP prophylaxis in addition to antiretroviral therapy.

FIGURE 1. Most recent CD4+ enumeration (within 60 days) prior to diagnosis of *Pneumocystis carinii* pneumonia (PCP) for 49 episodes occurring among HIV-infected patients

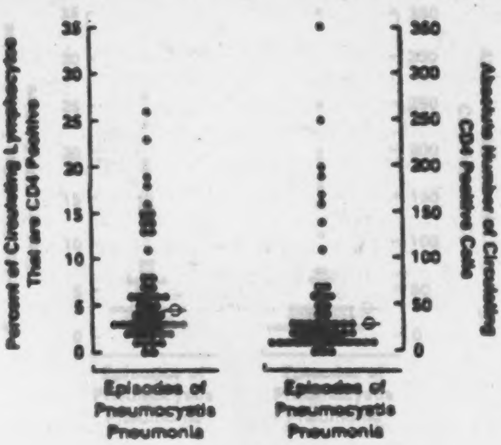
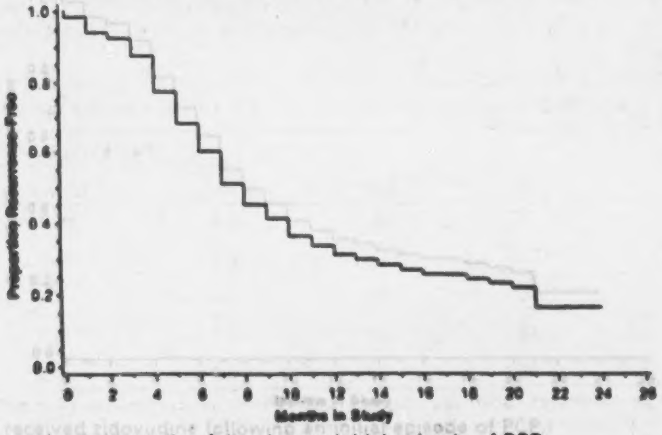


FIGURE 2. Kaplan-Meier life table probabilities of recurrent *Pneumocystis carinii* pneumonia (PCP) among patients on ACTG Protocol 002*



*All patients received zidovudine following an initial episode of PCP.

Times for patients who died without any subsequent episode of PCP are withdrawn at time of death.

REGIMENS FOR PROPHYLAXIS

The two compounds studied most extensively for prophylaxis against PCP have been trimethoprim-sulfamethoxazole, given orally, and pentamidine, given as an aerosol.

Trimethoprim-Sulfamethoxazole

The efficacy of trimethoprim-sulfamethoxazole for prophylaxis against PCP has been clearly demonstrated among pediatric cancer patients (*7-8*). The only reported randomized controlled trial of this drug combination for HIV-infected persons was a primary-prophylaxis study of 60 adult AIDS patients with Kaposi sarcoma, and compared the effect of no treatment with that of a regimen of 160 mg trimethoprim plus 800 mg sulfamethoxazole twice daily plus 5 mg leucovorin calcium once daily (*9*). Compared with untreated patients, those who received prophylaxis had fewer episodes of PCP and lived longer. Adverse reactions were common (50%) and included nausea, vomiting, pruritus, and rash, although these reactions also occurred commonly among patients who were not receiving trimethoprim-sulfamethoxazole. Only five patients (17%) had to discontinue prophylaxis. There are no results from controlled trials currently available for analysis to indicate whether trimethoprim-sulfamethoxazole would be effective or tolerated in other populations of HIV-infected patients.

Aerosol Pentamidine

Clinical studies of aerosol pentamidine for prophylaxis against PCP have been completed by two pharmaceutical sponsors. These studies have used different nebulizing devices and different dosing regimens.

In July 1987, a randomized, nonblinded dose-comparison study of aerosol pentamidine was begun in 14 community treatment centers (*10*). The trial was open to adult patients who had already had PCP (secondary prophylaxis) as well as patients with Kaposi sarcoma and other symptomatic HIV-associated conditions who had never had PCP (primary prophylaxis). Patients were randomly assigned to three dose schedules: 30 mg every 2 weeks, 150 mg every 2 weeks, or 300 mg every 4 weeks of pentamidine delivered by the Respirgard II jet nebulizer (Marquest, Englewood, CO).

An interim analysis 1 year after the start of randomization (mean follow-up of 10 months) showed that 76 PCP episodes (13 first episodes and 63 recurrent episodes) had occurred: 33/135 (24%) in the 30-mg group, 25/134 (19%) in the 150-mg group, and 18/139 (13%) in the 300-mg group. For patients receiving secondary prophylaxis, the regimen of 300 mg every 4 weeks was associated with substantially fewer episodes of PCP than the regimen of 30 mg every 2 weeks. There are insufficient data currently available from patients receiving primary prophylaxis to demonstrate statistically significant treatment effects among the regimens.

The most common adverse effects during treatment were cough and, less frequently, wheezing—particularly among smokers and patients with a history of asthma. These effects could be reduced or prevented by pretreatment with inhaled bronchodilators. No systemic toxicity of the type associated with parenteral pentamidine (e.g., renal insufficiency, hypoglycemia, or neutropenia) was detected, although other reports suggest that systemic adverse effects can occur. Patients tolerated the therapy well with supervision, and only two had withdrawn because of side effects at the time the interim analysis was done.

On the basis of these interim results and existing epidemiologic data from natural-history studies, the Food and Drug Administration approved a treatment IND for aerosol pentamidine as both primary and secondary prophylaxis, recommending the 300-mg dose every 4 weeks and recommending delivery via the Respirgard II jet nebulizer. The indication for primary prophylaxis in the treatment IND is a CD4+ count of <200/mm^3. Secondary prophylaxis is indicated for anyone who completes therapy for an episode of PCP.

Other nebulizers have been used in trials of aerosol pentamidine prophylaxis. A double-blinded, placebo-controlled randomized multicenter trial has recently been conducted in Canada which assessed the safety and efficacy of aerosol pentamidine administered by a Fisons ultrasonic nebulizer (five 60-mg loading doses followed by biweekly doses of 60 mg). These findings have been submitted to the FDA. A study using the Fisons nebulizer and three different doses of aerosol pentamidine has also been completed in the United States and is currently being evaluated.

RECOMMENDATIONS

On the basis of the data summarized above and the opinions of individual members of the panel of experts, the Public Health Service recommends that—unless contraindications exist—physicians should initiate prophylaxis against PCP for any HIV-infected adult patient who has already had an episode of PCP, even if the patient has been receiving zidovudine. Unless contraindicated, prophylaxis should also be initiated for HIV-infected patients who have never had an episode of PCP if their CD4+ cell count is <200/mm^3 or if their CD4+ cells are <20% of total lymphocytes. Patients with CD4+ cell counts of <100/mm^3 or CD4+ cells <10% and patients with oral thrush or persistent fever (temperature of >100°F) are at particularly high risk for PCP.

Patient Evaluation

For HIV-infected persons, CD4+ lymphocyte percentages or counts should be monitored at least every 6 months. Some experts prefer to obtain a second count within a few months of the first count to assess the rate of decline. Subsequent CD4+ enumerations may be desirable at intervals of <6 months in certain situations such as: a) the presence of fever or thrush, b) a recent rapid decline in CD4+ cell count, c) a CD4+ percentage in the 20-30 range, or d) a CD4+ absolute number in the 200-300/mm^3 range. If a decision to start prophylaxis is to be made on the basis of a low CD4+ cell count or percentage, the CD4+ enumeration should probably be repeated, unless previous determinations indicate the low count or percentage is consistent with an established trend.

Some patients may have discordant CD4+ percentages and absolute counts, i.e., the percentage may be >20% while the CD4+ count may be <200/mm^3, or vice versa. In such cases, it is probably prudent—after reconfirming the CD4+ enumerations—to assume that the patient is at high risk for PCP if either of these two parameters is in the high-risk range.

Clinicians should be aware that in certain unusual circumstances, either the absolute CD4+ count or the CD4+ percentage may not be an accurate reflection of susceptibility to PCP. For example, after splenectomy, HIV-infected patients may be susceptible despite normal CD4+ counts. Conversely, some laboratory reagents may not detect CD4+ markers on the T-helper cells of all persons (*11*), so that such persons may speciously appear to be in the susceptible range. In situations in which this phenomenon is suspected (e.g., when the sum of the number of CD4+ cells and CD8+ cells does not approximately equal the number of CD3+ cells), the lymphocyte sample should be retested with other CD4+ reagents.

Before prophylaxis against PCP is administered, patients must be evaluated to exclude certain active pulmonary diseases. If symptoms, signs, or radiologic abnormalities suggest that active disease is present, a thorough evaluation for community-acquired pathogens (e.g., *Pneumococcus*), opportunistic pathogens (e.g., *Pneumocystis,* cytomegalovirus), communicable pathogens (e.g., *Mycobacterium tuberculosis*), tumors, or other processes is indicated. As with other HIV-infected persons, these patients should be given a Mantoux skin test with 5-TU tuberculin, PPD (*12*).

Choice of Prophylactic Agent

Scientific studies available to date suggest the following two approaches are effective and safe, although neither has been approved as labelling indications by the Food and Drug Administration.

1) Although it has been studied less extensively among HIV-infected persons than aerosol pentamindine, oral trimethoprim-sulfamethoxazole (160 mg trimethoprim and 800 mg of sulfamethoxazole) can be given twice daily with 5 mg leucovorin once daily. This form of prophylaxis should not be given to patients with a history of type-I hypersensitivity (angioedema or anaphylaxis) or prior episodes of Stevens-Johnson syndrome associated with sulfonamides or trimethoprim. The efficacy of leucovorin in prevention of toxicity is unknown.
2) Aerosol pentamidine can be given as 300 mg every 4 weeks via the Respirgard II jet nebulizer. The dose should be diluted in 6 ml of sterile water and delivered at 6 liters/minute from a 50-PSI compressed air source until the reservoir is dry. (Further information can be obtained by telephoning the Treatment IND number: 1-800-727-7003.) Because other doses and aerosol delivery systems have not yet been adequately studied and analyzed, no recommendations regarding such systems can be made. For patients who develop cough or wheezing while receiving aerosol pentamidine, pretreatment with a bronchodilator can be tried before the aerosol therapy is given again. Patients with asthma or an extensive history of smoking may not tolerate this form of therapy, and it may not be prudent treatment for a patient with a prior life-threatening reaction to parenteral pentamidine.

Since neither aerosol pentamidine nor oral trimethoprim-sulfamethoxazole prophylaxis is known to be safe in association with pregnancy, it is inadvisable to give either agent to HIV-infected pregnant women. Rather, such women should be monitored carefully for symptoms, signs, or laboratory abnormalities suggestive of PCP. Prophylaxis can then be considered for use in the postpartum period. Careful monitoring is also indicated for patients intolerant of aerosol pentamidine and trimethoprim-sulfamethoxazole, or for those unwilling to receive prophylaxis.

Alternative regimens that are of unproven efficacy and safety for humans, but that might be considered for prophylaxis, include dapsone (daily or weekly), dapsone plus trimethoprim (daily or weekly), or dapsone plus pyrimethamine (daily or weekly) and pyrimethamine-sulfadoxine (weekly).

Follow-Up of Patients Receiving Prophylaxis

Since none of the regimens has been shown to be completely protective against PCP for HIV-infected persons, patients who receive prophylaxis should be monitored closely for evidence of PCP, as well as other pulmonary infections. If prophylaxis is discontinued, the patient will again be at increased risk for developing PCP.

Prophylaxis failures have been reported in which persons given aerosol pentamidine, especially at low doses, later had PCP in the upper lobes of the lung (13). In addition, prophylaxis using aerosol pentamidine does not offer protection against extrapulmonary pneumocystosis (14).

Prophylaxis for Infants and Children

Pneumocystis carinii pneumonia is a common manifestation of pediatric AIDS. Most experts agree that some form of prophylaxis is warranted for HIV-infected pediatric patients who are at high risk for PCP on the basis of criteria that are analagous to those described above for adults. However, there are insufficient data about the efficacy or toxicity of prophylactic regimens for pediatric patients, so that no scientifically validated guidelines can be provided as yet. There are no data concerning the appropriate dose or delivery system of aerosol pentamidine for infants or children. The appropriate dose of trimethoprim-sulfamethoxazole prophylaxis might be estimated from trials involving pediatric cancer patients (e.g., trimethoprim 75 mg/M^2 plus sulfamethoxazole 375 mg/M^2 given orally every 12 hours) (*7,8*).

Further Information

Several studies are under way to gain additional information about prophylaxis against PCP. Information about these studies can be obtained from the National Institute of Allergy and Infectious Diseases Information Office (1-800-TRIALS-A) or the American Foundation for AIDS Research (212-333-3118).

EDITORIAL COMMENTARY

These guidelines for prophylaxis against PCP indicate a medical benefit from the careful clinical and immunologic monitoring of persons infected with HIV and have several important implications. First, the guidelines are likely to increase the demand for HIV antibody testing by persons who believe they may be at risk for infection. The Public Health Service has estimated that between 945,000 and 1.4 million persons in the United States are infected with HIV (*15*). Of these persons, CDC estimates that approximately 120,000 have been informed of their infection status as a result of voluntary antibody testing carried out in public (primarily Federally funded) HIV counseling and testing centers. The number of persons found through other sources of testing to be infected is unknown, but it is likely that many persons who are infected are not aware of their infection. Persons at risk who have not had HIV antibody testing should now consider such testing because they may be candidates for prophylaxis against PCP if they are found to be infected.

Second, the guidelines are likely to increase the demand for medical services by asymptomatic HIV-infected persons. Such persons will need medical evaluation to determine whether they are candidates for prophylaxis against PCP, and – if prophylaxis is given – these persons will need medical follow-up. All persons found to be infected at HIV counseling and testing centers should be referred for further medical evaluation, including a measurement of their CD4+ cells. Facilities offering HIV counseling and testing should develop referral networks of medical-care providers sufficient to evaluate and care for the infected persons they identify. These networks should include services related to family planning and treatment for intravenous drug addiction, sexually transmitted disease, and tuberculosis.

Third, the guidelines are likely to increase the demand for flow-cytometry services to quantify CD4+ cells from HIV-infected persons. Laboratories to which samples are referred for flow cytometry should have prior experience, since methodology can greatly influence the quality of test results. Although there are no true reference standards for evaluating blood cells, quality can be assured by adhering to criteria that address sample collection, preparation, instrument calibration and standardization, flow cytometric analysis, and adequate training of operators (*16*). Either absolute CD4+ counts or percentage CD4+ cells can be used in monitoring HIV-infected persons. There appears to be less day-to-day fluctuation in percentage of CD4+ cells compared with absolute number, suggesting that the former measure may be more reliable (*4,17*). This finding is not unexpected since the percentage of CD4+ cells is directly measured by flow cytometry, whereas the absolute number is calculated from the absolute and differential white-blood-cell count and the percentage of CD4+ cells.

Fourth, health-care providers who administer aerosol pentamidine as prophylaxis against PCP should be aware of several occupational safety issues. In particular, they should note the recommendation to exclude active pulmonary disease before starting prophylaxis. A recent investigation of *M. tuberculosis* infections among the staff members of a health clinic in Florida suggested that one source of infection may have related to the use of aerosol pentamidine treatment for two patients who had positive sputum cultures for *M. tuberculosis* during the time they received aerosol pentamidine. One of these two patients coughed profusely both during and after therapy (*18*). Providers administering aerosol pentamidine should also review the manufacturer's instructions for the use of the nebulizer system. The Respirgard II nebulizer contains a filter designed to remove most of the pentamidine from exhaled gases. If the nebulizer is improperly used, substantial amounts of pentamidine can be released into the environment, and health-care workers or others in the vicinity may be at risk for the same adverse events as the patients who received the therapy (*19*).

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Lyphomed

Brian Tambi
Senior Vice President & General Manager
Ethical Pharmaceutical Division

January 19, 1990

Mr. James S. Benson
Acting Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD

Dear Mr. Benson:

In our letter of January 17, 1990 regarding the differences between the Lyphomed pentamidine protocol and that of Fisons plc, there was a major omission. As this omission greatly impacts cost of therapy, the basis of Senator Pryor's proposal, we thought it important to bring it to your attention.

The calculations on cost of therapy for the Fisons regimen in the hospital, physician clinic, and homecare setting did not take into consideration the fact that a "loading dose" is required as indicated by the Fisons' protocol* to initiate therapy. This loading dose requires that five (5) doses of 60 mg. nebulized pentamidine be given during the first two weeks of therapy. The bi-weekly doses begin seven (7) days following administration of the last loading dose. In effect, this translates into thirty (30) individual treatments over a one year period (52 weeks), as opposed to thirteen (13) under Lyphomed's approved regimen.

The economic impact of this loading dose requirement on the Fisons regimen is as follows (please refer to pages 8 and 9 of the January 17 correspondence):

* As reported in the Fisons presentation to the FDA Antiviral Drug Products Advisory Committee Meeting on May 1, 1989.

10401 West Touhy Ave
Rosemont, IL 60018-3302
312-390-6500
Telex: 206686
Fax: 312-390-1066

HOSPITAL CLINIC

	Lyphomed[1] Regimen 300 mg. q 4 weeks	Pisons[2] Regimen 60 mg. q 2 weeks
DRUG:	$99.45	$20.00 x 5 = $100.00[a] $20.00 x 1 = $ 20.00[b] $120.00[c]
EQUIPMENT:		
Nebulizer -	$ 6.00	$29.00 - $86.00[3]
Compressor -	N/A	N/A
LABOR:		
R.T.T. Time	$50 hr x 1 = $50	$50 hr x 5 = $250.00[a] $50 hr x 1 = $ 50.00[b] $300.00[c]
Rx Fee	$ 5	$ 5.00 x 5 = $ 25.00[a] $ 5.00 x 1 = $ 5.00[b] $ 30.00[c] $330.00[c]
MONTHLY COST:	$160.45	$479.00 - $536.00 (month 1) $179.00 - $236.00 (month 2-12)

DOCTOR'S CLINIC

	Lyphomed[1] Regimen 300 mg q 4 weeks	Pisons[2] Regimen 60 mg q 2 weeks
DRUG:	$99.45	$20.00 x 5 = $100.00[a] $20.00 x 1 = $ 20.00[b] $120.00[c]
EQUIPMENT:		
Nebulizer -	$ 6.00	$29.00 - $86.00[3]
Compressor -	$ 4.00[4]	N/A
LABOR:		
R.T.T. Time	$50 hr x 1 = $50	$50 hr x 5 = $250.00[a] $50 hr x 1 = $ 50.00[b] $300.00[c]
Rx Fee	$ 5	$ 5.00 x 5 = $ 25.00[a] $ 5.00 x 1 = $ 5.00[b] $ 30.00[c] $330.00[c]
MONTHLY COST:	$164.45	$479.00 - $536.00 (month 1) $179.00 - $236.00 (month 2-12)

HOMECARE

	Lyphomed[1] Regimen 300 mg q 4 weeks	Fisons[2] Regimen 60 mg q 2 weeks
DRUG:	$99.45	$20.00 x 5 = $100.00[a] $20.00 x 1 = $ 20.00[b] $120.00[c]
EQUIPMENT:		
Nebulizer -	$ 6.00	$29.00 - $86.00[3]
Compressor -	$20.00[5]	N/A
LABOR:	$100.00[6]	$100.00 x 5 = $500.00[a] $100.00 x 1 = $100.00[b] $600.00[c]
MONTHLY COST:	$225.45	$749.00 - $806.00 (month 1) $269.00 - $326.00 (month 2-12)

[a] first 2 weeks

[b] second and subsequent 2 week periods

[c] total for first 4 weeks

* For references 1-6, please see documentation in correspondence dated January 17, 1990.

SUMMARY OF ANNUAL COSTS

	LYPHOMED REGIMEN	FISONS REGIMEN
HOSPITAL CLINIC	$2,085.00	$2,627.00 - $3,368.00
PHYSICIAN CLINIC	$2,137.85	$2,627.00 - $3,368.00
HOMECARE	$2,930.85	$3,977.00 - $4,718.00

It is clear that the Lyphomed regimen, with single monthly administration, is far less expensive when compared to the Fisons regimen. The analysis does not include the patient compliance problems that would no doubt arise from Fisons' complicated regimen, nor the additional staffing requirements necessitated by the frequency of visits which would also add to the cost of total patient care.

Sincerely,

Brian Tambi

Brian Tambi

/dnt

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Characteristics of Nebulizers Used in the Treatment of AIDS-Related Pneumocystis Carinii Pneumonia

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ABSTRACT

To characterize aerosolized pentamidine delivery systems, we measured efficiency (drug inspired as percent of dose in nebulizer) and particle size distribution from several nebulizers under simulated clinical conditions. With a piston ventilator, radioactive tracers, and high performance liquid chromatography (HPLC), the Cadema *AeroTech II*, Marquest *Respigard II* and Fisons *Fisoneb* were tested. Each nebulizer was studied with the specific concentration of pentamidine and breathing pattern usually prescribed with the device. We found that each system delivered a significant fraction of respirable particles but there were important differences among nebulizers. With a tidal volume of 750 cc and frequency of 20 breaths/min, the *AeroTech II* produced a mass median aerodynamic diameter (MMAD) of 1.0 µm, $\sigma = 1.9$, efficiency = 21%; the *Respigard II* MMAD = 0.76 µm, $\sigma = 1.9$, efficiency = 4.6%; and the *Fisoneb* MMAD = 2.5 µm, $\sigma = 2.0$, efficiency = 16%. The *Fisoneb* was also tested at a frequency of 12 breaths/ min with an end-inspiratory breath-hold of 3.5 sec without significant changes in MMAD or σ. The size distribution of delivered aerosol was dependent on the type of nebulizer, tubing and attachments, breathing pattern, and presence of medication in the nebulizer. In clinical studies, these factors must be defined before efficacy of a drug can be assessed. Prescribing information should consider the delivery system and its efficiency to prevent inappropriately high or low levels of drug delivery.

INTRODUCTION

A recent clinical study demonstrating the effectiveness of aerosolized pentamidine as treatment for Pneumocystis carinii pneumonia (PCP) (Montgomery et al, 1987) has rekindled interest in aerosol therapy of lung infections. Patient awareness of pentamidine aerosol therapy coupled with the seriousness of PCP has led to widespread anecdotal use of the drug. However, variability between nebulizers has not been assessed. Furthermore, laboratory experiments to measure mass output and particle distribution of aerosol generators often utilize experimental conditions different from the clinical setting under which medical aerosol generators are used. Therefore, the purpose of the present

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KEY WORDS: AIDS, Pneumocystis pneumonia, aerosols, nebulizers, pentamidine.

study was to determine operating characteristics of various nebulizing systems commonly used to treat patients with PCP under conditions similar to those used in clinical practice. It should be recognized that the delivery system itself is not the only variable to consider in aerosol therapy. For example, in patients with cystic fibrosis, we found that the actual dose of aerosolized medication deposited in the lung was dependent on several factors of equal importance including pulmonary function, breathing pattern and the performance of the nebulizer (Ilowite et al, 1987). Presently, there are no similar data available in patients with PCP and studies are underway. In the meantime, recognition of the differences in presently available nebulizing systems will help in evaluating clinical efficacy.

METHODS

Principles

Polydisperse nebulizing systems are often characterized by measuring the particle size distribution of the "standing cloud", that is, the aerosol expressed from the nebulizer via the jet used to drive the nebulizer or, in the case of ultrasonic systems, a small internal fan or the suction flow from a cascade impactor. The "output" can be defined gravimetrically as the loss in weight of the nebulizer or the change in volume of the nebulizer solution over time (Phipps et al, 1987; Dahlbäck et al, 1986; Brain and Valberg, 1979). These techniques assume negligible effects on aerosol distribution and output from attachments between the nebulizer and patient, changes in fluid properties from dissolved medications, and changes in the breathing pattern of the patient. Preliminary studies in our laboratory suggested that the above assumptions may not be correct. Many nebulizers depend on baffles and other attachments to regulate size distribution. Surface tension in ultrasonic generators is important. Therefore, it may be necessary to measure the performance of the nebulizer during actual use conditions with tubing in place and medication present in proper dose.

Efficiency

The experimental configuration for each nebulizer is illustrated in Fig.1 (A-C). Each nebulizer and its specific attachments required for clinical use was connected to the Harvard piston ventilator at the site of the patient mouthpiece. Interposed between the nebulizer tubing and the ventilator was an absolute filter of low resistance defined as the "inspiratory filter". During inspiration, this filter is presented with the aerosol that would ordinarily be inhaled by the patient. With a radioactive tracer (Technetium pertechnetate (^{99m}Tc)) originally mixed in the nebulizer with a solution of pentamidine or saline, the nebulizer efficiency can be defined as the fraction of the initial activity in the nebulizer deposited on the inspiratory filter. If the radioactivity in the aerosol accurately reflects aerosolized pentamidine, this efficiency represents the fraction of pentamidine originally placed in the nebulizer that would be inhaled by a patient breathing at the same frequency and tidal volume set on the ventilator.

Efficiency of the *Respigard II* was also measured using ^{99m}Tc-human serum albumin (^{99m}Tc-HSA, MediPhysics, Paramus, N.J., 2.1 mg), and ^{99m}Tc-sulphur colloid (^{99m}Tc-SC, CIS/US, Lake Success, N.Y.,0.1cc) as the radioactive labels. These were tested because the ^{99m}Tc pertechnetate which was used for the laboratory testing of nebulizers is freely permeable to the lung and not suitable for deposition studies. The other compounds do not readily enter the blood when deposited in the lung and are frequently used in clinical studies. However, they have different physical properties than pertechnetate and they may not reflect the delivery of aerosolized drug if they behave differently in the nebulizer.

Particle distribution

To assess the distribution of particle sizes in the aerosol, a ten stage cascade impactor (Delron Research, Powell, Ohio) was connected in line just upstream to the inspiratory filter. In a series of experiments separate from the efficiency measurements, the radiolabelled aerosol was sampled at 1.0 l/min with the ventilator on or off (standing cloud). During ventilated nebulization, the inspiratory filter caught all the particles in the inspiratory stream that are not sampled by the cascade and there were no particles in the exhaled air from the ventilator. Therefore, the cascaded

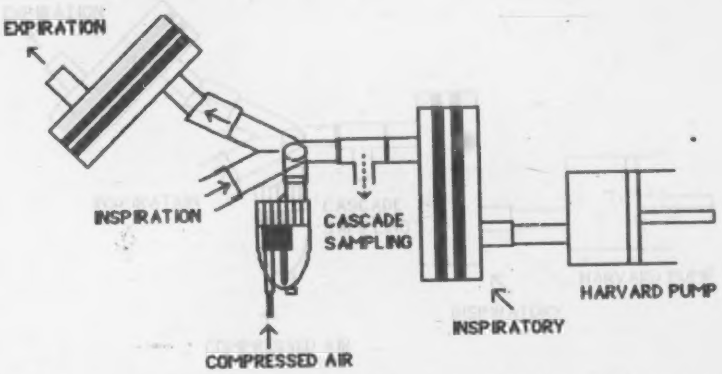
EXPIRATION
INSPIRATION
CASCADE SAMPLING
HARVARD PUMP
INSPIRATORY
COMPRESSED AIR

FIGURE 1A: Diagram of the *AeroTech* II. The arrows indicate one-way valves. The expiratory filter is supplied by the manufacturer, the inspiratory filter is of our own design with removable paper allowing measurement of radioactivity. Both are of low resistance.

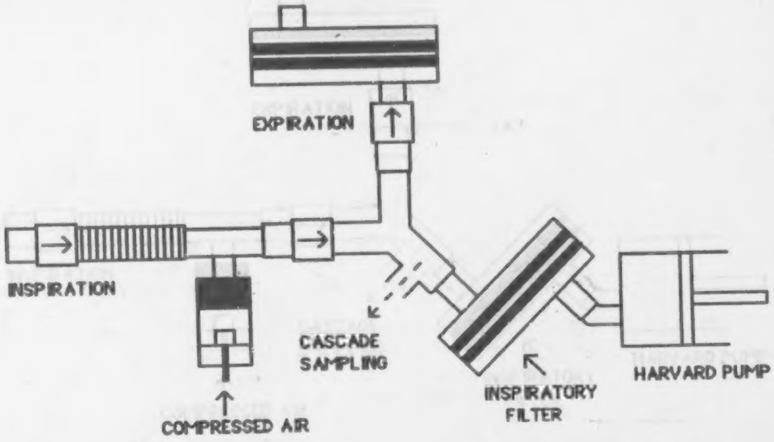
EXPIRATION
INSPIRATION
CASCADE SAMPLING
HARVARD PUMP
INSPIRATORY FILTER
COMPRESSED AIR

FIGURE 1B: The *Respigard* II. The tubing arrangement supplied by the manufacturer includes a one way valve between the nebulizer and the patient mouthpiece. The expiratory filter is supplied with the nebulizer. The *AeroTech II* and the *Respigard II* operate continuously. Aerosol generated during expiration is captured by the expiratory filters

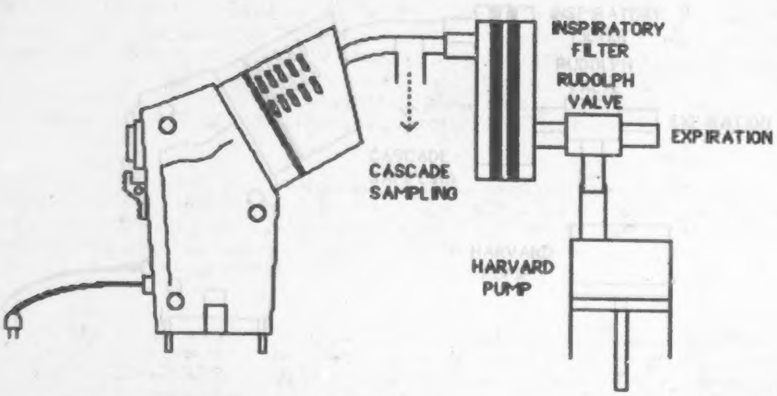

FIGURE 1C: The *Fisoneb*. This ultrasonic nebulizer has a small internal fan that moves the aerosol from an inner chamber to the tubing containing the patient's ventilatory stream. For all experiments the rheostat governing this flow was set on "min", its lowest setting. The nebulizer is actuated manually only during inspiration. Patients are instructed to exhale through their nose or to disconnect from the mouthpiece after each inhalation. To duplicate this pattern we installed the Rudolph valve which separates the inspiratory and expiratory streams from the ventilator and prevents exhalation into the nebulizer. No expiratory filter is supplied.

sample represents only the inhaled aerosol distribution. With the ventilator disconnected, the aerosol passes out of the nebulizer carried by the jet (AeroTech II and Respigard II) or the internal fan (Fisoneb) for measurement of the standing cloud. For each nebulizer, serial cascades were performed at intervals during nebulization to evaluate aerosol distribution throughout the period of aerosol delivery.

Experimental protocol

Breathing pattern: To compare different nebulizers, and measure the effects of other variables, it is necessary to standardize the breathing pattern. In clinical studies, during aerosol inhalation, patients are usually instructed to breathe in a relaxed "tidal" manner. Therefore, we used a tidal volume of 750 cc and a frequency at 20 breaths per min. These values were chosen based on the optimum pattern observed in our previous study in patients with cystic fibrosis (Ilowite et al, 1987). Patients with PCP may breathe differently but data on their behavior is presently unavailable. All three nebulizers were tested using this pattern. Because the *Fisoneb* has been reported to be used at a frequency of approximately 12 breaths per minute followed by a 3.5 sec breath-hold (NIH protocol ACTG 069), that nebulizer was tested with both patterns.

The following conditions were fixed for each system (sources are listed):

AeroTech II: 4cc distilled water, 10 l/min flow, 50 PSI, 300mg pentamidine (LyphoMed, Rosemont, Ill.), running time (to dryness) 15 min. (Cadema Medical Products Inc.).

Respigard II: 6cc distilled water, 6 l/min flow, 50 PSI, 300mg or 600mg pentamidine (LyphoMed), running time of 20 min (NIH protocol ACTG 040), this leaves 2-3 cc of the original solution in the nebulizer).

Fisoneb: 3cc (1 ampule) solution of 60 mg pentamidine (Fisons, Bedford, MA.), flow setting on 'min', nebulizer actuated manually only on inspiration, running time (to dryness) 6 min. (Fisons Corporation and NIH protocol ACTG 069).

In addition to the conditions described above the following experiments were performed to further investigate the peculiarities of each system.

"Standing cloud" aerosol distribution; i.e. the distribution without the Harvard pump ventilating the system. Each nebulizer was run completely assembled as in Fig. 1 but the aerosol sampled was delivered to the cascade by the gas running the nebulizer (or the internal fan in the case of the *Fisoneb*). All nebulizers were filled with 0.9% saline for these experiments.

Respigard II without tubing and valve attachments; of all the tested systems, the *Respigard II* has the most complicated inline attachments (Y piece and one-way valve between nebulizer and patient). The nebulizer was studied alone, with the one-way valve, and with all attachments to determine possible effects on aerosol distribution.

Aerosol distribution and efficiency with and without pentamidine added to the solution. These experiments illustrate the tendency of a given nebulizer to be affected by the active drug.

HPLC analysis

When aqueous solutions are nebulized, the solutes often are concentrated due to evaporation and, in addition, some may be adsorbed onto surfaces of the nebulizer walls. To insure that the radiolabel behaved in a manner similar to the drug, we analyzed the nebulizer solution serially for pentamidine and radioactivity during typical experimental runs. Each specimen was analyzed by scintillation counting for radioactivity and pentamidine by HPLC. HPLC was performed using a Perkin-Elmer Model MPF-44B using methods described by Lin et al, 1986. 10 µl samples were taken of the nebulizer fluid at periodic intervals and related on a percentage basis to time = 0 (100 %). The results were averaged and converted to percentages of the initial values at time = 0. The mean percents of the radioactivity measurements were compared to the mean percents of the HPLC pentamidine determinations by paired t test. Significance was assigned a p value of ≤ 0.05.

RESULTS

Nebulizer efficiency

The relationship between inspired aerosol and running time for each nebulizer is shown in Fig. 2. Activity on the inspiratory filter was serially sampled at fixed intervals over the prescribed running time. Each nebulizer produced particles at a constant rate over most of the running time. The *Fisoneb* and *AeroTech II* are actually nebulized to dryness and their production tends to plateau towards the end of the run. The *Respigard II* has a relatively low production rate and because of patient fatigue its use is limited to 20 min (NIH protocol ACTG 040). Therefore the *Respigard II* aerosol generated is linear over the entire running period and when shut off the nebulizer chamber still contains approximately 2-3 cc of fluid. The total aerosol captured on the inspiratory filter as a percent of the initial activity placed in the nebulizer defines each unit's efficiency.

Efficiency data for all experiments are shown in Table 1. Each run represents data from a separate nebulizer except for the *Fisoneb* data, which were obtained from a single ultrasonic nebulizer.

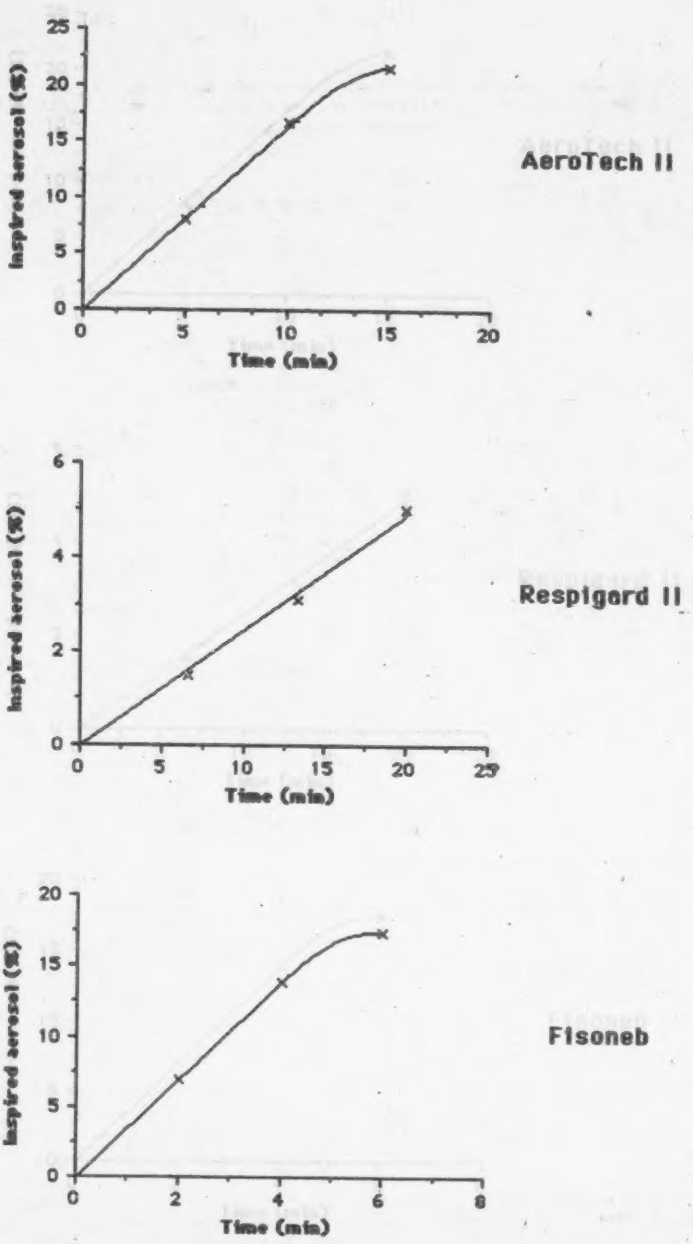

FIGURE 2: Inspired Aerosol vs Running Time. Cumulative radioactivity deposited onto the inspiratory filter by the Harvard pump as a percent of initial nebulizer activity as a function of time. The final value at the end of the run represents the nebulizer's efficiency.

TABLE 1

Nebulizer outputs under various experimental conditions.
Unless indicated otherwise, all runs are at a tidal volume of 750 cc and a frequency of 20/min.

RUN #	EFFICIENCY (%)	EXPERIMENTAL CONDITIONS
AEROTECH II		
1	19	300 mg pentamidine
2	22	300 mg "
3	22	saline
4	21	saline
RESPIGARD II		
1	3.2	600 mg pentamidine
2	6.2	600 mg "
3	5.0	600 mg "
4	3.6	600 mg " labelled with HSA
5	3.8	300 mg "
6	6.0	300 mg "
7	3.9	saline
8	3.0	saline
9	0.46	600 mg pentamidine labelled with SC
10	0.52	600 mg " labelled with SC
11	0.70	600 mg " labelled with SC
FISONEB		
1	14	60 mg pentamidine
2	17	60 mg "
3	16	saline
4	12	saline
5	15	frequency = 12, 3.5 sec BH, 60 mg pent.
6	19	frequency = 12, 3.5 sec BH, saline

HSA: ^{99m}Tc-human serum albumin, 2.1 mg.
SC: ^{99m}Tc-sulphur colloid, 0.1cc.
For all isotopes, the activity placed in the nebulizer ranged between 0.5 and 9.0 mCi.

Under the conditions described above, with pentamidine in solution, the *AeroTech II* and *Fisoneb* deliver approximately 21 and 16 %, respectively, of the original activity to the inspiratory filter. The *Respigard II*, however, is much less efficient delivering on the average 4.6 % for solutions containing pentamidine. Efficiency does not appear to be affected by the presence of the drug. When the *Fisoneb* is operated at a lower respiratory frequency, the efficiency is still in the same range as the "standard" breathing pattern.

Also listed on Table 1 are the efficiencies measured when the ^{99m}Tc-HSA and ^{99m}Tc-SC were substituted for ^{99m}Tc-pertechnetate. Efficiency measured by ^{99m}Tc-HSA (3.6%) was similiar to the routine pertechnetate value. For the sulphur colloid experiments, however, efficiency as assessed by radioactivity was greatly diminished and averaged 0.56 % (see DISCUSSION).

Particle distribution

Particle distributions for each nebulizer under simulated clinical conditions are shown in Fig.3. Each measurement was made with pentamidine in solution. Particle size is plotted on a log scale (ordinate) vs probability (abcissa). If the aerosol distribution is log-normal, the graph should be a straight line. The distributions only approximate a straight line and the values of σ were estimated by reading the particle diameter at 16 % cumulative probability and dividing that value by the MMAD. The *Respigard II* and *AeroTech II* produce similar aerosols with the MMAD equal to 0.77 (σ = 1.9) and 1.1 µm (σ = 1.9) respectively. The *Fisoneb* MMAD was somewhat larger at 2.5 µm (σ = 2.0). For the slower breathing frequency of 12/min, the *Fisoneb* produced a similar aerosol (2.0 µm (σ = 1.9)). In Fig. 4, both *Fisoneb* distributions are compared. They are essentially the same.

All measurements are summarized in Table 2. A variety of experiments were performed to test the peculiarities of each system.

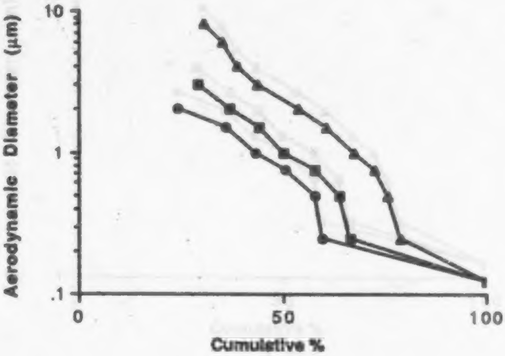

FIGURE 3: Distribution of particle sizes for *Fisoneb* (triangles), *AeroTech II* (rectangles), and *Respigard II* (circles) under simulated clinical use conditions.

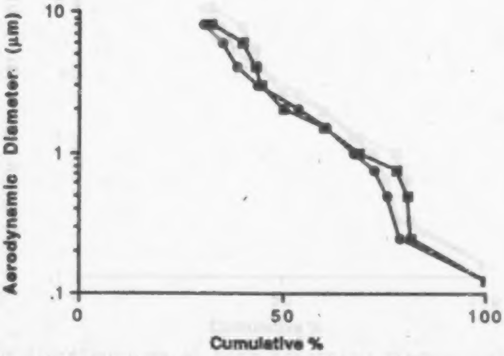

FIGURE 4: *Fisoneb* distributions at both breathing frequencies. Frequency = 20 (circles), frequency = 12, 3.5 sec breath hold (rectangles).

TABLE 2

Aerosol distributions measured under various experimental conditions. Unless indicated otherwise, all runs are at a tidal volume of 750 cc and a frequency of 20/min. The period of measurement using the cascade impactor varied for each nebulizer because of differences in efficiency. To assess possible changes in aerosol distribution over the entire running time, serial cascades were performed over specified time intervals (a & b experiments).

RUN #	MMAD (µm)	σ	EXPERIMENTAL CONDITIONS
AEROTECH II			
1	1.0	1.9	300 mg pentamidine
2	1.1	1.9	300 mg "
all runs listed below are with saline and ^{99m}Tc-pertechnetate only			
3a	1.0	1.9	standing cloud, 0-3 min
3b	1.0	1.9	standing cloud, 3-6 min
4	0.90	2.0	
5a	0.60	2.1	0-5 min
5b	0.76	2.0	10-15 min
6a	0.64	1.7	0-5 min
6b	0.64	1.7	10-15 min
7a	0.66	1.7	0-5 min
7b	0.66	1.7	10-15 min
RESPIGARD II			
1	0.77	1.9	600 mg pentmidine
2	0.72	1.8	600 mg " HSA
3	0.78	1.8	600 mg " HSA
4	0.75	1.7	300 mg "
5a	0.78	2.0	300 mg " 0-10 min
5b	0.78	2.0	300 mg " 10-20 min
all runs listed below are with saline and ^{99m}Tc-pertechnetate only			
6	0.25	NA	
7	0.25	NA	
8a	0.25	NA	0-10 min
8b	0.25	NA	10-20 min
9a	0.56	1.5	standing cloud (H-pump off)
9b	0.25	NA	H-pump on
10a	1.2	2.4	T piece only (H-pump off)
10b	0.68	1.6	T piece + 1-way valve
10c	0.62	1.6	Y piece added
FISONEB			
1	2.5	2.0	60 mg pentamidine, 0-4 min
2	2.1	1.4	saline, 0-1 min
3	2.3	1.7	saline, 0-5 min
4	5.3	2.0	saline, standing cloud 0-1 min
all runs listed below are at a frequency of 12 and a breath hold of 3.5 sec			
5	3.2	2.1	60 mg pentamidine
6	2.0	1.9	60 mg "
7	2.0	1.9	60 mg "
8	0.80	NA	saline
9	0.88	NA	saline

NA: bimodal distribution, σ cannot be calculated.

AEROTECH II

A small but reproducible effect of the drug itself on particle distribution was noted. Without pentamidine, the aerosols were somewhat smaller (between 0.60 & 0.90 μm; runs 4-7) than those obtained with pentamidine in solution (1.0-1.1 μm, runs 1 & 2) indicating the addition of the drug increased the size of the aerosol. The standing cloud (runs 3a & 3b) is larger than the saline aerosol produced during ventilation with the Harvard pump (runs 4-7). Serial cascade determinations performed on the same nebulizer over different periods during the prescribed total nebulization run demonstrated that the aerosol distribution did not significantly change during the standard delivery time period.

RESPIGARD II

The presence of pentamidine had a greater effect on the *Respigard II*. Runs 1-5 indicate pentamidine aerosols in the range of 0.72-0.78 μm. Saline aerosols were significantly smaller at 0.25 μm (runs 6-8). In addition, the distribution of the saline aerosols cannot be approximated by a single value of σ because their distributions were more bimodal (Fig. 5). Like the *AeroTech II*, the *Respigard II* is supplied with one-way valves to separate the inspiratory and expiratory streams of airflow but, for the *Respigard II*, the expiratory valve is inline between the nebulizer and the patient. These appear to effect the final aerosol distribution. As pictured in Fig. 1B, the *Respigard II* attachments between the nebulizer and the patient include a T piece, a one-way valve and the final Y connection. In run #10a, the standing cloud from the nebulizer and the T piece was measured at 1.2 μm. With the one way valve added, the MMAD decreased to 0.68 μm (10b). The Y piece had little added effect (MMAD = 0.62, 10c). With the Harvard pump ventilating the assembled system the particle size was reduced from 0.52 μm (standing cloud) to 0.25 μm (runs 9a-b). The aerosol distribution did not change during the period of nebulization as mesured by serial cascades (runs 5a-b & 8a-b). Finally, the addition of HSA to the solution (2.1 mg) did not affect the distribution (runs 2 & 3).

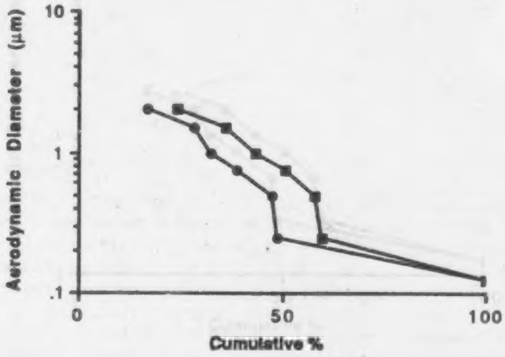

FIGURE 5: *Respigard II* distributions; with pentamidine (600 mg, rectangles); without pentamidine (saline, circles).

FISONEB

With pentamidine in solution, the breathing pattern did not appear to affect the final aerosol distribution (run 1 compared to runs 5-7). However, saline aerosols were more sensitive to ventilation, with a bimodal aerosol of 0.80-0.88 μm produced at a frequency of 12, breath hold 3.5 sec (runs 8 & 9)

which contrasted with the same solution ventilated at 20/min (MMAD 2.1-2.3, runs 2 & 3). The standing cloud was much larger with the MMAD equal to 5.3 µm (run 4). Timed cascades did not show any changes in aerosol distribution during the treatment period (runs 2 & 3). The effect of pentamidine on the final aerosol distribution for the slower breathing frequency is shown in detail in Fig. 6. Under these conditions, the *Fisoneb* is more sensitive to breathing pattern and the presence of pentamidine. However, under clinical delivery conditions, all the *Fisoneb* aerosols with pentamidine present are similar.

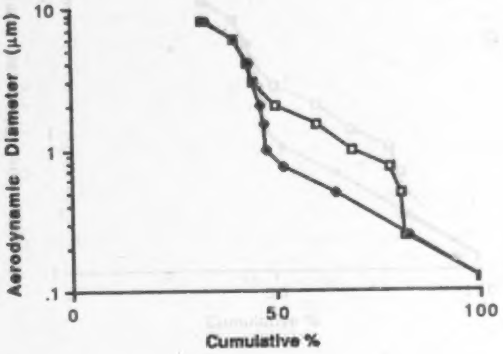

FIGURE 6: *Fisoneb* distributions, frequency = 12; with pentamidine (60 mg, open rectangles), without pentamidine (saline, filled rectangles). The saline aerosol appears bimodal.

HPLC measurements

Fig. 7 demonstrates the changes in concentration of ^{99m}Tc-pertechnetate and pentamidine during nebulization. For each nebulizer, three separate runs were performed with duplicate samples for each time indicated in Fig. 7 (6 pairs for statistical analysis). The level of precision for the radioactive and pentamidine assays is indicated by the narrow standard deviation bars at time = 0. The *AeroTech II* and *Respigard II*, both jet nebulizers, concentrated both radioactivity and pentamidine. For the *AeroTech II*, no significant differences were found between pentamidine and the pertechnetate label. However, at 10 min, near the end of the run, the experimental variation increased, probably due to unstable operation as the solution ran out. The ***Respigard II*, however, is not run to dryness and operation appears more stable.** Under these conditions, small but statistically significant differences between the radiolabel and pentamidine were seen with pentamidine more concentrated than pertechnetate. Correction of the efficiencies listed in Table 1 for these differences would not be more than 5-10% of the listed values. The *Fisoneb* does not concentrate its solution with time and no differences were measured between pentamidine and pertechnetate.

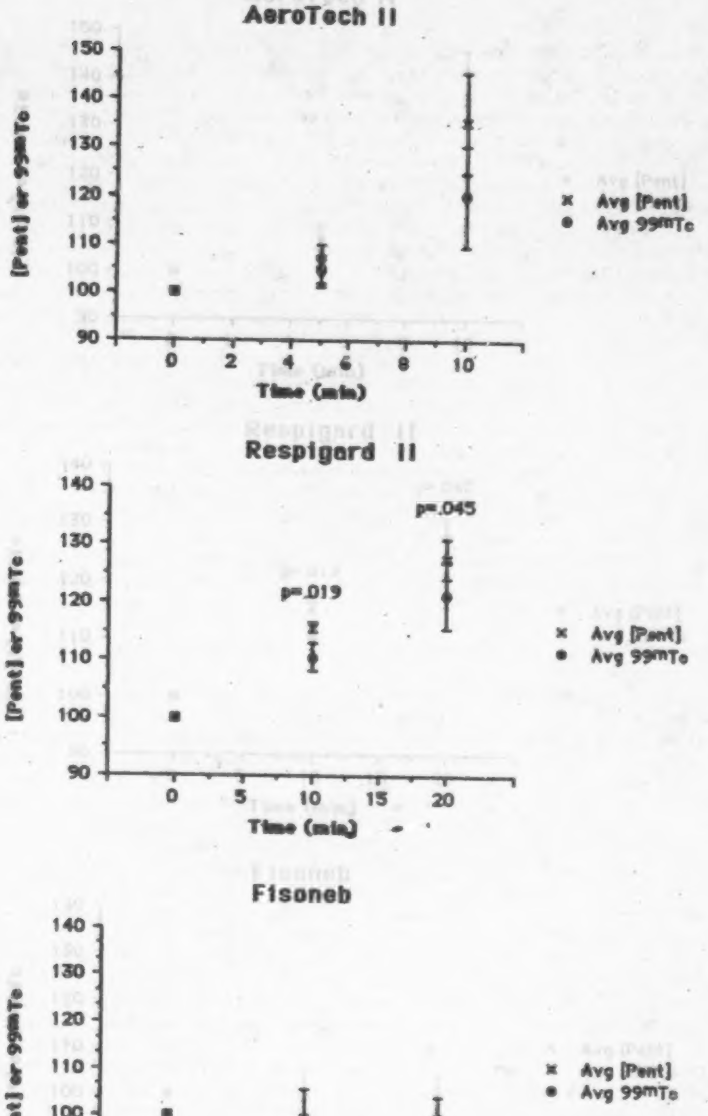

FIGURE 7: Simultaneous measurement of radioactivity (^{99m}Tc) and pentamidine concentration as percents of initial values.

DISCUSSION

The present paper demonstrates that the type of nebulzer, its attachments, and the mode of aerosol delivery can result in important differences in the quantity of inhaled drug and the size distribution of inhaled particles. Standard laboratory techniques to measure aerosol distribution and nebulizer output may not be adaquate to predict drug delivery in clinical use. For example, the *Fisoneb* produced a MMAD of 5.3 µm when aerosolized saline was presented to the cascade impactor by its internal fan. When the same system was ventilated using patterns mimicking actual clinical conditions the observed MMAD decreased to 2.5 µm. The dependency of particle size on nebulizer attachments, illustrated with the *Respigard II* data, precludes the substitution of different tubing and valves in clinical use. Otherwise, the aerosol distribution cannot be guaranteed. Of equal importance was the effect of added medication. In every case, the addition of pentamidine increased particle sizes and often changed the overall distribution. This effect was most pronounced for the *Fisoneb* and may be related to the dependence of ultrasonically produced aerosols on surface tension (Brain and Valberg, 1979).

Efficiency can vary by several fold among nebulizers. This fact may be clinically important. For example, using Montgomery's treatment regimen, 600 mg of pentamidine nebulized for 20 min via the *Respigard II* would deliver approximately 27.6 mg of pentamidine to the patient (600 x 0.046). To deliver an equivalent amount of pentamidine using the *AeroTech II*, the dose in the nebulizer should be reduced to 135 mg, reflecting the differences in nebulizer efficiency.

The differences between the ^{99m}Tc pertechnetate, HSA and SC radiolabels shown in Table 1 demonstrate the importance of confirming the parallel behavior of a label and the active drug. All the data used to assess nebulizers in the present paper were determined with ^{99m}Tc-pertechnetate. If we had used ^{99m}Tc-SC, a compound commonly used in human aerosol studies, *Respigard II* efficiencies would have been grossly underestimated. Well-counter determinations of residual radioactivity in the nebulizer indicated that a large proportion of the colloid remained in the nebulizer and may have been adsorbed onto plastic surfaces. ^{99m}Tc-HSA, however, appeared to behave similarly to the pertechnetate and is probably suitable for patient studies with the *Respigard II*. These experiments were preliminary and were performed to illustrate that even isotopic labels need to be characterized for each system. Before using the albumin label, the activity-pentamidine concentration curves must be determined as they were done for pertechnetate in Fig 7.

The points mentioned above provide a framework for clinical evaluation of aerosolized medication, but, laboratory testing is only a first approximation towards a thorough understanding of the behavior of an aerosol delivery system. For aerosolized antibiotics, a satisfactory clinical result may be dependent on the amount of local deposition and sites of infection and these needs will vary with different diseases. Clearly, the amount of drug actually delivered is important, and yet it is rarely considered in clinical protocols. Further, patient factors that influence lung deposition are of equal significance. Even with adaquate delivery, the aerosol may fail to deposit because of patient related factors. Presently, only a single quantitative study measuring these factors in a clinical population is available. In patients with cystic fibrosis, Ilowite et al (1987) measured total and regional deposition of aerosolized gentamicin, with a fixed MMAD and σ, and found that sites of deposition were strongly dependent on the underlying mechanical state of the patient's lung. Further, the total deposition in a given patient was a complex function of the breathing pattern. An optimum breathing pattern was found that was a function of changing nebulizer output combined with changing breath by breath lung deposition. These observations could not be predicted from laboratory tests of the nebulizer alone or from physiological studies of aerosol deposition. We should emphasize that Ilowite's study, as well as the present paper, do not set standards for clinical aerosol use. They provide a better understanding of drug delivery and lung deposition. The clinical importance of the factors discussed above remains to be demonstrated. Quantitative pilot studies in patients should be performed for a given clinical situation to determine the range of lung dose, sites of deposition, acute toxicities and other factors that could be important in interpreting the results of large scale clinical trials.

ACKNOWLEDGMENTS

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Selective Delivery of Pentamidine to the Lung by Aerosol[1-3]

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ELISA N. BRUNETTE, EMIL T. LIN, and PHILIP C. HOPEWELL

SUMMARY In 8 patients with diffuse infiltrates on chest radiograph undergoing fiberoptic bronchoscopy for suspected *Pneumocystis carinii* pneumonia, bronchoalveolar lavage sediment and supernatant concentrations of pentamidine were compared 18 to 24 h after administration of 4 mg/kg intravenous (n = 3) and aerosolized (n = 5) pentamidine isethionate. Aerosol was inhaled for 35 to 40 min with 300 mg of pentamidine isethionate in a jet nebulizer, baffled to decrease the particle size to 1.42 μm ± 1.88 (mass median aerodynamic diameter ± geometric standard deviation). Bronchoalveolar pentamidine concentrations were: in sediment, 8.24 ± 1.76 postintravenous versus 705 ± 242 ng/ml postaerosol (mean ± SEM, $p < 0.05$); supernatant, 2.64 ± 0.73 postintravenous versus 23.2 ± 7.75 ng/ml postaerosol (mean ± SEM, $p < 0.05$). Serum pentamidine levels were low or undetectable after aerosolization. Aerosol administration delivers significantly higher concentrations of pentamidine to the air spaces than does intravenous delivery in patients with diffuse alveolar infiltrates.

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Because of high frequency of adverse reactions to current standard therapy for *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome (AIDS), development of new approaches to treatment is of considerable importance (1–4). Recently, it has been shown that in normal mice, high pulmonary concentrations of pentamidine are present 48 h after aerosol administration (5). Moreover, aerosolized pentamidine has been demonstrated to be effective as treatment or prophylaxis in the rat pneumocystosis model and effective therapy for *P. carinii* pneumonia in patients with AIDS (6–8). We describe here a device to generate and deliver pentamidine aerosol to humans. Using this device, we have shown that high alveolar concentrations of the drug are produced with little systemic uptake in patients with suspected *P. carinii* pneumonia. Administration of pentamidine in the form of an aerosol directly into the lungs has the potential of being both effective and well tolerated because of the intra-alveolar location of the organism and because systemic absorption is minimal.

The system (Respigard II; Marquest, Englewood, CO) used to generate and deliver the pentamidine aerosol is shown in figure 1. A compressed oxygen (5 to 7 L/min at 345 kPa, 50 psi) powered nebulizer produces the aerosol, and one-way valves provide for entrainment of room air in patients whose minute ventilation is high, act as a baffle to decrease particle size, and direct expired air to a filter that removes the remaining particles of drug, thereby preventing environmental contamination.

The size of pentamidine particles was determined in 3 locations: (*1*) immediately distal to the nebulizer (point A in figure 1), (*2*) from the stream passing the mouthpiece (point B in figure 1), and (*3*) distal to the exhalation filter (point C in figure 1). Particles were sized with a 7-stage Mercer cascade impactor (Intox Products, Albuquerque, NM). The gas supply was 6 L/min, the sample stream was not dried, and the impactor flow rates were 0.5 L/min. Concentrations of pentamidine from the impactor plates after eluting with 10 ml of sterile water were determined by optical density at 262 nm and compared with standard curves. Results from the average of 3 determinations at each location were expressed as mass median aerodynamic diameter ± geometric standard deviation (MMAD ± GSD) (9).

Any patient 18 yr of age or older with or suspected of having AIDS who was hospitalized for fiberoptic bronchoscopy to evaluate diffuse infiltrates on chest radiograph was eligible for this study. The study protocol and consent form were approved by the Committee on Human Research of the University of California, San Francisco.

Two groups of patients were studied. The first group consisted of 3 patients who had been given empiric intravenous pentamidine (4 mg/kg) prior to bronchoscopy. Two patients had received 1 dose and the other had received 3 doses. Five other patients were given a single exposure to an aerosol of pentamidine for 35 to 40 min. Three hundred mg of pentamidine isethionate (LyphoMed, Melrose Park, IL) dissolved in 6 ml of sterile water was aerosolized until the nebulizer was empty. In the aerosol group, blood samples were drawn before and 15, 30, 60, 120, and 180 min and 24 h after administration of pentamidine. Eighteen to 24 h later, both groups underwent fiberoptic bronchoscopy. After inspection of the airways, 3 to 5 20-ml aliquots of normal saline were injected and aspirated from the right middle lobe until at least 40 ml were recovered (10). Lavage fluid was centrifuged at 1,000 × *g* for 10 min at 10° C. Pentamidine concentrations in the lavage supernatant, sediment, and blood serum were analyzed by methods previously described (5, 6, 11). Briefly, proteins were precipitated with acetonitrile containing the internal standard hexamidine. After purification with a C-8 bond elution cartridge column (Analytichem, Harbor City, CA), pentamidine was separated by high performance liquid chromatography, and concentrations were determined by comparison to a standard curve for the drug and to hexamidine as an internal standard (6, 11). Pentamidine concentrations were expressed as ng/ml of either blood or BAL fluid. The lower limit of sensitivity of the assay was 2 to 3 ng/ml. A two-sample *t* test was used to compare groups; p values of < 0.05 were regarded as significant.

Pentamidine particle size distal to the nebulizer was 2.38 μm ± 2.31 (MMAD ± GSD), with greater than 20% of the mass of particles being larger than 4 μm. At the mouthpiece, the particle size was 1.42 μm ± 1.88 (MMAD ± GSD), with less than 5% of the mass of particles larger than 4 μm. The mean MMAD of pentamidine in the airstream immediately distal to the nebulizer (point A in figure 1) was larger than in the airstream passing the mouthpiece (point B in figure 1) ($p < 0.002$ by two-sample *t* test). No pentamidine was found distal to the exhalation filter.

Pentamidine concentrations in BAL supernatant and BAL sediment 18 to 24 h after either aerosol or intravenous administration for all patients in both groups are shown in table 1. Concentrations were greatest in BAL sediment in the aerosol group, exceeding those found in BAL sediment from the intravenous group by 10- to 100-fold. The mean BAL supernatant concentration in the aerosol group exceeded the sediment concentration in the intravenous group by a factor of more than 2. Of all the serum samples drawn in the aerosol pentamidine group, only one patient in the aerosol group had a measurable amount of pentamidine in serum (13 ng/ml in Patient 5 at 30 min). All 3 patients in the intravenous group and 3 of 5 patients in the aerosol group were found to have *P. carinii* pneumonia. All patients infected with *P. carinii* responded to standard therapy with either intravenous pentamidine or sulfamethoxazole-trimethoprim.

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This study demonstrates that 18 to 24 h af-

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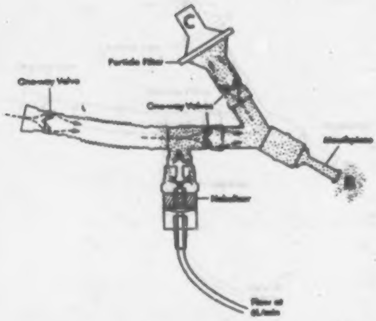

Fig. 1. Diagram of nebulizer and delivery system for pentamidine aerosol. A, B, and C were sample sites for particle size determination.

ter administration, aerosolized pentamidine produces significantly higher concentrations of the drug in the lung than are produced by intravenous injection. Little or no systemic absorption was detectable. In contrast, mean peak serum pentamidine concentrations using an identical assay in patients with AIDS and *P. carinii* receiving a single 4-mg/kg dose of intravenous pentamidine are 612 ng/ml (12). Although adverse reactions to pentamidine have not been correlated with its concentration in blood, very low concentrations of the drug in blood may greatly reduce its effects on organs other than the lungs. In an open trial of aerosolized pentamidine for *P. carinii* pneumonia in patients with AIDS, systemic adverse reactions did not occur. The only adverse reaction was cough, presumably from airway irritation (8). It is not known whether pentamidine, the sulfite in isethionate, pH, or other factors are responsible for this airway irritation. However, other sulfite-containing compounds cause significant airway constriction in asthmatics at doses 100-fold less than the concentration of sulfite used in these studies (13). A larger particle-sized aerosol would lead to increased airway deposition and might increase airway toxicity (14).

Exactly where in the lung the pentamidine was deposited could not be determined by our study. Performing BAL 18 to 24 h after administration of the aerosol should have allowed enough time for the drug to have been cleared by the mucociliary system, thereby suggesting predominantly alveolar deposition as would be predicted from the size of the particles generated (14). It is possible, however, that in the presence of lung inflammation and edema, mucociliary clearance was slowed and that some of the material obtained by lavage was derived from the airways. The finding that concentrations of pentamidine are much greater in BAL sediment than in supernatant is consistent with the drug being taken up by cells within the air spaces. In patients with *P. carinii* pneumonia, BAL sediment is predominantly alveolar macrophages, although other cells may have contained pentamidine (15).

The variability of BAL pentamidine levels after aerosolization is not surprising. We did not control for breathing patterns or severity of disease, and both may affect aerosol deposition (14). In addition, interpatient differences in pentamidine clearance may occur; marked variability of pentamidine serum levels has been reported after intravenous administration (12).

In conclusion, using this aerosol device, high pulmonary and low systemic concentrations of pentamidine in patients with diseased lungs can be achieved when compared with intravenous administration. The particle size and output of nebulizers used in clinical trials will need to be characterized for meaningful comparisons of adverse reaction rates and dose.

TABLE 1

PENTAMIDINE CONCENTRATIONS FROM BRONCHOALVEOLAR LAVAGE

	BAL Supernatant (ng/ml)	BAL Sediment (ng/ml)
Intravenous administration		
Patient 1	1.48	12.8
Patient 2	2.44	6.88
Patient 3	4.8	8.35
Mean ± SEM	2.84 ± 0.73	9.34 ± 1.74
Aerosol administration		
Patient 1	21.8	140
Patient 2	23.4	141
Patient 3	43	1067
Patient 4	5.1	851
Patient 5	*	1326
Mean ± SEM	23.2 ± 7.75†	705 ± 242†

* Unable to measure because of unidentified interfering substance.

† $p < 0.05$ compared with intravenous group.

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Reviews, Overviews, & Updates

Aerosolized Pentamidine for Treatment and Prophylaxis of *Pneumocystis carinii* Pneumonia: An Update

Kevin J Corkery BS RCP RRT, John M Luce MD, and A Bruce Montgomery MD

Introduction

The rapid increase in numbers of cases of *Pneumocystis carinii* pneumonia (PCP) in patients with the acquired immunodeficiency syndrome (AIDS) has led to a search for effective and less toxic antipneumocystosis therapy and prophylaxis. This short review is intended to summarize recent developments regarding aerosolized pentamidine and inspire further research in this promising modality.

Background

The first reports of *P. carinii* causing what was then known as interstitial plasma cell pneumonia originated in central Europe in the 1940's in infants suffering from malnutrition. Subsequently, PCP was diagnosed in patients with impaired host immunity, leading to the classification of the organism as an opportunist.[1] With few exceptions, PCP continued to be a sporadic opportunistic infection involving mainly patients who had lymphomas or leukemias or who were receiving immunosuppressive therapy.[1] Beginning in 1979, however, the epidemiology of PCP changed drastically with the development of the AIDS epidemic. Since that year, more than 49,000 AIDS cases have been reported to the Centers for Disease Control (CDC).[2] *P. carinii* pneumonia is the most common life-threatening opportunistic infection reported among patients with AIDS. It is the initial opportunistic infection in 65% of HIV-infected patients and occurs in 20% of patients whose diagnosis of AIDS has been established by another process. An analysis of past trends projects a cumulative AIDS incidence of 270,000 by 1991, with 51,000 new cases occurring in that year alone.[3,4] Hence, it is projected that, by 1991, more than 173,000 cases of PCP will have occurred in the United States alone.

Pneumocystis carinii pneumonia in AIDS patients may have protean manifestations but classically presents with symptoms of fever, cough, and dyspnea.[1] Diagnostic tests characteristically reveal arterial hypoxemia, diffuse radiographic infiltrates, and evidence of restrictive lung disease.[1] Unlike common pathogens that cause bacterial pneumonia, *P. carinii* is an extracellular protozoan that inhabits predominantly the alveolar spaces, with close approximation to the surfaces of alveolar epithelial cells or alveolar macrophages.[5] Extrapulmonary *P. carinii* infections are rare, suggesting that the alveolar environment is usually necessary for growth of the pathogen.[5] Optimal therapy would produce adequate antipneumocystosis drug levels in alveoli while limiting systemic side effects, this being the theoretical advantage of aerosol therapy that targets the lungs.

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Conventional and Experimental Systemic Therapy

Two drugs, trimethoprim-sulfamethoxazole (TMP-SMX) and pentamidine isethionate, have been conventional therapy for PCP. TMP-SMX is administered intravenously (I.V.) or orally, whereas pentamidine isethionate is usually administered I.V. or intramuscularly (IM).[6] Both intravenous pentamidine and TMP-SMX are at least 80% effective in the treatment of first-time episodes of PCP in patients with AIDS.[7] However, both conventional therapies have a 50% or greater incidence of adverse reactions that necessitate a change in drug therapy.[7-9]

Common adverse reactions seen with administration of TMP-SMX involve rash, fever, nausea, leukopenia, thrombocytopenia, and hepatitis.[7,9] The adverse effects of parenteral pentamidine include pain, swelling, and sterile abscesses at the site of IM injection, and thrombophlebitis and urticarial eruptions with I.V. administration.[10,11] Severe hypotension may develop with a single IM dose or after rapid I.V. infusion.[10,11] Hypoglycemia has been reported in up to 62% of patients;[11] subsequent diabetes mellitus occurs rarely.[12] Impaired renal function has been described in up to 25% of patients receiving systemic pentamidine.[11,12] Other side effects attributed to pentamidine include elevated liver enzymes, neutropenia, thrombocytopenia, fever, hypocalcemia, hallucinations, arrhythmias, and pancreatitis.[12]

Although not approved by the Food and Drug Administration (FDA), oral dapsone-trimethoprim has been shown to be as effective as, but less toxic than, oral TMP-SMX in AIDS patients with first-time episodes of PCP of mild severity in both a pilot study[13] and a double-blind trial.[14] The adverse reactions seen with dapsone-trimethoprim are nausea, vomiting, skin rash, decreased hematocrit, elevated creatinine, methemoglobinemia, elevated liver enzymes, neutropenia, and thrombocytopenia.[13,14]

Trimetrexate is another experimental agent for PCP that has been approved by the FDA for use on a compassionate basis. Trimetrexate is a potent inhibitor of mammalian and protozoal dihydrofolate reductase.[15] Due to its solubility in lipids, this agent easily enters both the protozoan and mammalian cells. Folinic acid (leucovorin) must be administered as a specific antidote to protect host tissues from toxic antifolate effects.[16] Leucovorin, which is not lipid-soluble, is actively transported into mammalian cells but not into *P. carinii* cells.[15] A pilot study with trimetrexate-leucovorin and trimetrexate-leucovorin with sulfadiazine revealed a 70% positive-response rate.[16] Adverse reactions were less severe in the trimetrexate-leucovorin therapy than in conventional therapy, but they were similar to the reactions to TMP-SMX in patients receiving trimetrexate-leucovorin with sulfadiazine.[16] Adverse reactions seen with trimetrexate-leucovorin are neutropenia, thrombocytopenia, elevated creatinine, elevated liver enzymes, and rash.[16] Particularly promising results were seen in salvage therapy after failure to respond to standard therapy. Eleven of 16 patients survived, a considerable improvement compared with what has been reported in similar patients in other studies. Patients who received trimetrexate-leucovorin alone as initial therapy had a significant relapse rate of PCP within 6 weeks of ending therapy.[16]

Aerosol Pentamidine Therapy

Because of the high frequency of adverse reactions seen with current therapies for PCP, novel therapies are needed. Two approaches are possible: use new agents as noted earlier or target delivery of known agents. Due to the intra-alveolar location of *P. carinii*, aerosolization of pentamidine should provide an effective, site-specific, and hence less-systemically toxic method of therapy[17,18] or prophylaxis.[19] Studies of aerosolized pentamidine in rats with PCP have documented efficacy in both prophylaxis and treatment and suggest that the half-life of the drug is long—probably weeks with increased clearance in ill animals.[17-19] Debs and colleagues reported negligible clearance in 48 hours in normal mice,[17] in rats the elimination half-life from the lungs has been reported to be 36 days.[20] A recent study of prolonged tissue concentrations after parenteral administration in AIDS patients suggests that an effective aerosol-delivery device should achieve high lung concentrations of pentamidine.[21]

Pentamidine has been nebulized only as a heterodispersed aerosol. Aerosol size is described by mass median aerodynamic diameter (MMAD), and the size range is described by geometric standard deviation. MMAD is defined as the particle size such that half the mass of the aerosol is contained in larger particles and half in smaller particles.[22] Geometric standard deviation is a unitless measurement calculated by dividing the MMAD by particle size at the 84th percentile of the total mass.[23] Generally, a geometric standard deviation greater than 2 indicates a wide range of particle sizes.[23] The size range of pentamidine aerosols that have been used clinically has varied from 0.25 to greater than 12 μ (Table 1).

Aerosol deposition is determined by three interdependent processes—inertial impaction, gravitational sedimentation, and Brownian motion—each affecting different size ranges of particles.[22,23,25-27] Inertial impaction occurs at areas of nonlaminar flow in the oropharynx and large central airways. Nonlaminar conditions are created by turns and bifurcations or increased flowrates. Larger particles generally impact from inertia in the oropharynx; almost all particles > 10 μ do not reach the alveoli, and most are impacted in the oropharynx. Likewise, the majority of particles > 5 μ do not reach beyond the central airways. The second process, gravitational sedimentation, is determined by low-flow states of particles between 0.5 and 10 μ in small airways and alveoli. Brownian motion, the third process of particle deposition, causes particles < 0.5 μ to deposit randomly throughout the lung. The relatively large surface area of alveoli compared to airway surface area determines that more submicronic particles deposit in the alveoli.[22,23,25-27] Approximately 80% of particles in this size range remain suspended and are exhaled.[23,27]

Particle size, therefore, is a major determinant of location of deposition. The optimal size of particles for alveolar deposition is between 1 and 2 μ, and for tracheobronchial deposition it is between 4 and 7 μ.[23] Many patient factors affect aerosol deposition, including inspiratory flowrates, frequency of respiration, breath-holding, and tidal volumes. Airway narrowing from bronchospasm, emphysema, mucus,

Table 1. Features of Nebulizers Used To Deliver Aerosolized Pentamidine

	MMAD* (μ)	GSD†	Reservoir for Aerosol during Exhalation?	Expiratory Filter?	Comments
Jet Nebulizers					
Aerotech II	2.0	± 2.5‡	No	Optional	10-15 L/min flow
Centimist	1.1	± 2.2§	Yes	No	9 L/min flow
Fan Jet	4.3	± 2.5‡	No	Optional	7 L/min flow
Respirgard II	0.93	± 1.8‡	Yes	Yes	7 L/min flow
System 22	1.3||	N.A.	No	No	7 L/min flow
Ultra Vent	0.25	± 2.0¶	No	Yes	11-14 L/min flow
Ultrasonic Nebulizers					
Fisoneb	5.0	± 2.0‡	Yes	No	Intermittent use trigger
"Green Machine"	> 12.0	N.A.	Yes	No	Intermittent use trigger
Portasonic	1.6	± 2.2‡	Yes	Optional	Continuous flow
Pulmosonic	4.2	± 2.3‡	Yes	No	Continuous flow

*MMAD = mass median aerodynamic diameter. This was measured by noted methods under various conditions and may not be directly comparable.

†GSD = geometric standard deviation.

‡Particle size measured as in Ref 31, with 7 L/min flow to jet nebulizer or to flush chamber on ultrasonic nebulizer.

§Particle size measured under conditions of simulated breathing (Ref 24).

||Particle size measured by Malvern 2400 laser diffraction particle sizer (Ref 34).

¶Particle size measured by cascade impactor (Ref 29).

N.A. = not available (not noted or not measured).

and/or alveolar-filling processes such as PCP also can limit aerosol delivery to the alveoli.[22,25,26]

Two types of nebulizers, ultrasonic and jet, have been employed to deliver aerosolized pentamidine. Ultrasonic nebulizers operate by generating an ultra-high-frequency sound from a piezoelectric crystal that creates a geyser from which particles are expelled.[28] The particle size of aerosols from ultrasonic nebulizers is a function of the frequency of the signal to the piezoelectric crystal[28] and of flowrates. A higher frequency ultrasonic nebulizer will produce smaller initial particles, but when flow through the nebulizer is discontinuous, as with tidal breathing, larger particles are created because the small particles rapidly coalesce into larger particles.[23] It will not be surprising if different measurements of output and particle size are reported, because of different operating conditions. Jet nebulizers work by high-flow gas shearing liquid strands from a thin layer of solution maintained by surface tension. The liquid strands hit a baffle, and a wide variety of particle sizes is created. The larger particles generally fall by gravity and are reincorporated into the solution. Smaller particles can be created by higher gas pressures. Due to the inherent continuous flow, output, and particle-size distribution, jet nebulizers are relatively more constant than ultrasonic nebulizers.[28]

Commercially available ultrasonic nebulizers currently in use are the Fisoneb, Pulmosonic, and Portosonic (Table 1).* The Fisoneb and Pulmosonic both operate at a frequency of 1.3 mHz, which predicts a MMAD of 4 to 6 μ.[28] The Pulmosonic has been reported to deliver few particles < 2 μ and therefore may be unsuitable for applications requiring high yields to peripheral lung areas.[29] The Portosonic nebulizer is a 2.3-mHz ultrasonic nebulizer and may offer the combination of a 1.3 μ MMAD with a high output. Output and particle size of ultrasonic nebulizers need to be periodically sampled, as the frequency of the piezoelectric crystal may alter with age.[29]

Nebulizers are commercially available in the United States that produce a MMAD between 0.25 and 2.0 μ (Table 1). The Respirgard II, currently used in studies at San Francisco General Hospital, has one-way valves that control a drug reservoir, that allow entrainment of room air in patients whose minute ventilation is high, that act as a baffle to decrease particle size, and that direct expired air to a filter that scavenges remaining drug, preventing environmental contamination. The Cantimist is a similar device with a larger reservoir but no expiratory filter. The Aerotech II has internal baffles in the jet nebulizer and therefore may allow recycling of the drug; however, because it requires a high gas flowrate between 10 and 15 L/min and lacks an aerosol reservoir, much of the drug is not available to the patient for inhalation. Experience with the Aerotech II is limited. Although efficacy is not known, anecdotal reports of coughing at high doses above 100 mg have led to use of a 40-mg dose for prophylaxis studies (Tom Boylen MD: personal communication.) Three factors could account for the increased incidence of airway reactivity at higher doses: increased flows from the higher inherent flowrate of the device, a larger particle size, or higher output from the nebulizer. The Ultra Vent has a MMAD of 0.25 μ.[29] This would predict random deposition by Brownian motion throughout the lung, with most of the particles being exhaled.[25,27]

The present state of knowledge cannot allow determination of the most effective device because comparative pharmacokinetic studies have not been conducted in human beings. The device should maximize alveolar deposition and keep large-airway deposition to a minimum because pentamidine isethionate, containing a SO_3 moiety, is an airway irritant.[30] The optimal particle size for alveolar deposition is between 1 and 2 μ, with 1 μ achieving more peripheral distribution and less airway distribution.[22,23,25–27] Other features such as reservoirs, operating flowrates, and external filters may also be important.

A pharmacokinetic study that allows estimates of the dose of pentamidine needed in treatment trials using the Respirgard II has been conducted in eight patients with diffuse alveolar infiltrates undergoing fiberoptic bronchoscopy for suspected PCP.[31] Bronchoalveolar lavage (BAL) sediment and supernatant concentrations of pentamidine were compared between 18 and 24 hours after administration of 4 mg/kg IV (n = 3) and aerosolized (n = 5) pentamidine isethionate to different groups of patients. An aerosol containing 300 mg of pentamidine isethionate in 6 ml of distilled water was inhaled for 35 to 40 minutes. In patients with diffuse alveolar infiltrates, significantly higher concentrations of aerosolized pentamidine reached the airspaces than did the I.V. form of the drug; BAL pentamidine concentrations in sediment were 9.34 ± 1.74 ng/ml post-I.V. administration vs 705 ± 242 ng/ml post-aerosol (mean ± SEM, $P < 0.05$).[31] Serum pentamidine levels were low or undetectable after aerosolization. The large variation in BAL levels following aerosol but not I.V. administration suggests that the variability is due to aerosol deposition and not to BAL technique.[31]

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*Suppliers are identified in the Product Sources section at the end of the text.

Conte and colleagues, using another aerosol device (the Ultra Vent nebulizer), have conducted a similar study and reached similar conclusions.[32] The efficiency of the two nebulisers in the studies could not be directly compared due to different methods of BAL analysis.

Three pilot studies of aerosolized pentamidine as treatment have been conducted. In one study,[33] Montgomery and colleagues used 600 mg of pentamidine in the Respirgard II nebulizer in order to at least match the dose used in the pharmacokinetic study cited earlier[31] and to shorten the duration of therapy. Montgomery et al had noted that aerosol administration for longer than 30 minutes was not well tolerated and that the nebulizer became progressively less efficient. They estimated the deposited dose to be between 30 and 60 mg because the nebulizer probably delivers about 5 to 10% of the dose to the lungs.[22] In this study, 15 AIDS patients with initial episodes of mild to moderate PCP received a 25-minute daily inhalation of aerosol pentamidine for 21 days. Thirteen of the 15 patients responded to therapy. In successfully treated patients, mean P_{aO_2} was 67.9 torr before therapy and 80.1 torr after therapy; mean vital capacity was 50.8% of predicted value before therapy and 67.9% of predicted value after therapy. No adverse systemic reactions (such as renal, liver, and hematologic abnormalities, hypoglycemia, or hypotension) were observed during therapy. Serum pentamidine concentrations were less than 10 ng/ml in 12 of 14 patients. In two patients, serum pentamidine concentrations were 22 and 32 ng/ml at the end of therapy. Coughing was noted in 12 patients and was successfully treated in 9 patients by administration of an aerosolized bronchodilator prior to aerosolization of pentamidine or by lowering the gas flowrate to the pentamidine aerosol delivery device.[33] Three patients who had persistent cough had a history of bronchospasm or smoking.[33] After one year of follow-up, only two relapses have occurred.

In a second study, Conte and colleagues studied inhaled or reduced-dose pentamidine for treatment of PCP.[32] Nine of the 13 patients inhaling aerosolized pentamidine for treatment of mild PCP had a satisfactory response in this study; three patients could not be evaluated due to early withdrawal, and one had treatment failure. Two of the nine patients who could be evaluated had neutropenia, but these patients had been receiving zidovudine (azidothymidine, AZT) and had low pretreatment leukocyte counts. Other mild adverse reactions involved cough, bronchospasm, rash in one patient, and temperature elevations. The nebulizer (Ultra Vent) dose was 4 mg/kg body weight; this was nebulized over a 30- to 60-minute period.[32] Serum pentamidine concentrations were greater than 20 ng/ml in 5 of 13 patients. The higher serum pentamidine concentrations in this study as compared to that of Montgomery and colleagues are unexplained but may be due to the increased airway deposition, resulting in systemic absorption. Three of the successfully treated patients experienced early relapse.[32] Based on dose, duration of treatment, particle size, deposition estimates, higher nebulizer flowrate, and lack of a nebulizer reservoir, the total dose delivered to the alveoli in this study was probably one half to one fourth the dose used by Montgomery and colleagues; whether this explains the difference in patient outcome in the two studies is not known.

The third study was by Godfrey-Faussett and colleagues.[34] An acorn nebulizer (System 22) that lacks a drug reservoir was used with or without a bead filter at two different doses in 13 patients (4 mg/kg in the first 6 patients and 8 mg/kg in the other 7 patients). Only two patients responded; the others were removed for failure to respond or cough. The MMAD of aerosol from their nebulizer system was 1.3 μ for the first 10 patients and 0.8 μ for the remainder. They concluded that the optimum characteristics of the best delivery system need to be determined prior to recommendation that aerosolized pentamidine be used for treatment.[34]

Other side effects of aerosolized pentamidine therapy include hypoglycemia, reported in one patient after receiving 5 days of a daily 300-mg dose of aerosolized pentamidine with the Respirgard II nebulizer system.[35] The degree of hypoglycemia was much milder than that commonly seen with parenteral pentamidine, and it resolved after 9 days despite continued aerosol administration.[35]

Conventional and Experimental Systemic Prophylaxis

Because relapse of PCP in AIDS patients is a problem of enormous magnitude, cost, and mortality, an effective and nontoxic prophylactic intervention would be of great benefit. Analysis of 74 consecutive patients with first-episode PCP at San Francisco General Hospital has shown the probability of a second PCP episode to be 18% at 6 months, 46% at 9 months, and 65% at 18 months.[36] Hence, most AIDS patients with a first episode of PCP who do not die from other causes will relapse within 18 months.[36] A 10 to 50% mortality rate has been reported with first-episode PCP.[7,8,11,12,36] At San Francisco General Hospital, the first- and second-episode figures are 20% and 37%, respectively (David Feigal MD: personal communication).

Uncontrolled or unblinded trials of various therapeutic regimens, including oral TMP-SMX,[37] oral Fansidar,[38] oral dapsone,[39] and parenteral pentamidine[40,41] in AIDS patients have been reported to decrease the recurrence of PCP compared with historical controls.

TMP-SMX provides effective prophylaxis against PCP in children receiving chemotherapy when given twice daily every day[42] and three days per week.[43] The children on the thrice-weekly regimen had a lower incidence of systemic fungal infections, but other toxicity was similar. Although previous investigators have had difficulty in administering chronic TMP-SMX to patients with AIDS or AIDS-related complex (ARC) because of dose-limiting toxicity, including nausea, vomiting, rash, fever, or marrow suppression,[44] a regimen of twice daily TMP-SMX plus folinic acid was recently shown to provide effective primary prophylaxis for Kaposi's sarcoma patients undergoing chemotherapy.[37] Half these patients suffered minor toxicity and 17% suffered dose-limiting toxicity. The investigators continued to treat despite the appearance of a rash, a frequent reason for noncompliance and abandonment of prophylaxis in the previous trial.[37,44] The generalization of these findings to patients after their first episode of PCP or receiving AZT is unclear. Many post-PCP AIDS patients may have been sensitized to sulfa agents during their treatment for PCP,[7,9] and dose-limiting cytopenias commonly occur in patients on AZT [45] and in HIV-infected persons on TMP-SMX.[46] Therefore, dose-limiting toxicity may be much more common in patients on the combination of AZT and TMP-SMX than that observed in the study by Fischl and colleagues.[37]

Other prophylactic therapies have been studied. Another antifolate combination, Fansidar (25 mg pyrimethamine plus 500 mg sulfadoxine), administered once weekly has been studied at UCLA.[38] After a mean follow-up time of 11 months (range: 3 to 27 months) only 5 of 60 patients had a second episode of PCP. In six patients, Fansidar was discontinued because of rash. Anecdotal reports of lack of efficacy and of Steven-Johnson syndrome have led to difficulty in conducting prospective trials of this agent.[47]

Pentamidine (4 mg/kg administered IM or I.V. once monthly) has also been used as prophylaxis in patients who had previously received pentamidine for treatment, with promising results.[40,41] The efficacy of dapsone as secondary prophylaxis of PCP in a controlled trial has not been reported, but a recent abstract on a large open trial reports efficacy.[39]

Aerosol Pentamidine Prophylaxis

For aerosolized pentamidine to be effective as prophylaxis, the correct dose and time interval to maintain adequate lung levels of drug must be known. Dose-ranging studies comparing different doses and time intervals are underway in San Francisco. Leoung and colleagues have been studying 438 patients in three groups: prior PCP (n = 250), Kaposi's sarcoma (n = 59), and ARC (n = 129).[48] Patients have been randomized to receive either 30, 150, or 300 mg of aerosolized pentamidine, using the Respirgard II Nebulizer System. The 30- and 150-mg doses have been administered every 2 weeks, the 300-mg dose every 4 weeks. Combining data from all three doses, Leoung and colleagues have detected 12 episodes of PCP, 10 of which represent relapses, and two of which are first episodes in the ARC group. Historical case controls have been available for 152 patients following their first episode of PCP, matched for time from the episode. The number of relapses in the control group has been 37, compared to 6 in the 152 patients receiving aerosolized pentamidine ($P < 0.01$).[48] The efficacy over longer periods and toxicity other than airway irritation of each dosing group have yet to be determined.

In another San Francisco study, Fallat and colleagues have treated 211 patients with a dose of 30 mg of aerosolized pentamidine delivered by the Fan Jet nebulizer.[49] These investigators have estimated that relapse was delayed an average of 5 months in their patients.[49] Lowery and colleagues have reviewed the radiographic pattern of relapse in patients on aerosol pentamidine and found a striking increase of relapses in the upper lobes.[50] This correlates with the predicted deposition of most of the drug in the lower lobes and suggests that patients respond to the aerosol. In order to achieve more even distribution of the aerosol throughout all lung zones, it may be efficacious to have the patient breathe at a fast rate, breathe higher doses, and/or periodically breathe from residual volume during the aerosol administration.[50]

Other data on aerosol prophylaxis have been reported by Bernard and colleagues from Sloan Kettering Medical Center.[51] Aerosolized pentamidine has been administered using a Siemens "Green Machine"* hand-held ultrasonic nebulizer in this protocol. In the first trials, 30 mg of pentamidine was administered bi-weekly; in the next set of trials, patients were randomized to 30, 45, or 60 mg weekly for the first month and then bi-weekly.[51] The 30- and 45-mg doses were discontinued because of prophylaxis breakthrough. They reported that a total of 120 patients with AIDS and PCP had been treated for an average of 5 months. Five episodes of PCP have been reported in patients receiving 30 mg, two episodes in patients receiving 45 mg, and one episode in patients receiving 60 mg.[51] It is unclear how much of the pentamidine actually reached the lung periphery of these patients since the "Green Machine" ultrasonic nebulizer used in this study produces a median particle size > 12 μ (Table 1). Because of this large particle size, most of the drug probably is delivered to the oropharynx.[22,25,26] Bernard and colleagues are now doing dose-ranging studies with a Fisoneb ultrasonic nebulizer.

The optimal dose, particle size, and frequency of administration for prophylactic aerosol pentamidine are not known. A change in the distribution, severity of occurrence, and frequency is apparent even at low doses delivered to the alveoli, but whether higher doses prove more efficacious without significant side effects is yet to be determined. It will be difficult to compare specific doses with those achieved at other centers using different nebulizers because the amount of pentamidine deposited in the alveoli is so dependent upon equipment and patient factors. Furthermore, uncontrolled studies may involve patients with different rates of relapse because the incidence of recurrent PCP is dependent on time between episodes of PCP and the start of prophylaxis.[12]

Administration

Lypholized pentamidine must be reconstituted with sterile water, because saline solutions cause the pentamidine to precipitate out of solution. We have chosen the volume of the diluent to be 6 ml because 100 mg/ml is the saturation concentration, and also to standardize therapy. After reconstitution, pentamidine is stable at 20°C for 24 hours, at 4°C for 104 hours, and at −10°C for 5 months (Abu Alam PhD, LyphoMed Inc: unpublished data).

We cannot comment on other nebulizer systems used to deliver aerosolized pentamidine because we have personal experience with only the Respirgard II Nebulizer System. However, if one uses the Respirgard II Nebulizer System, the nebulizer flowrate should be 5-7 L/min using a pressure-compensated flowmeter attached to a 50-psi dry-gas source; this generates a nebulizer-line pressure of 20 to 25 psi. If the 50-psi dry-gas source is not available for prophylactic administration of non-acutely ill patients, we recommend the BIRD BA 400 air compressor or equivalent with a variable pressure (20-50 psi) regulating knob. The Respirgard II Nebulizer System should be attached to a PALL BB50-I nebulizer-line bacterial filter or equivalent, which is attached to a nipple adapter on the oxygen DISS connector of the air compressor. The variable-psi knob must be adjusted between 23 and 25 psi to match the pressure found using the dry-gas source distal to the flowmeter. Because the nebulizer output per unit of time decreases at pressures less than 20 psi, we do not recommend the use of small home compressors for the administration of aerosolized pentamidine. Aerosolization of pentamidine requires consistent and accurate regulation of flow and pressure in order to achieve ideal particle sizing for maximal alveolar deposition. We recommend that respiratory care practitioners stay in attendance during the course of the therapy. If the patient should want to take a break or starts coughing, the practitioner should turn off the gas flow to the nebulizer to prevent pentamidine from being aerosolized to the open environment. Studies of the effect of second-hand aerosolized pentamidine on healthcare personnel have not been performed. However, the Respigard II Nebulizer System effectively scavenges pentamidine when used properly.[31]

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*"Green Machine" is a nickname bestowed on the device by researchers, not a commercial name. The nebulizer is not available in the U.S., and Siemens would not recognize the name.

Risks of Aerosol Pentamidine

The complications experienced by patients in the studies to date include bronchospasm, fatigue, burning sensation in the back of the throat, mild hypoglycemia, and unpleasant taste. Severe cough is noted in some patients who have a history of asthma or smoking.[32-35] If cough or bronchospasm occurs, therapy should be interrupted and a bronchodilator administered. Subsequent therapy in patients with cough will require a bronchodilator before administration of pentamidine. For mild cough, in some instances lowering the gas flowrate to 4-5 L/min has helped. A few patients with acute PCP have experienced fatigue during therapy; in these instances, one should allow the patient to take breaks during the treatment. Some patients experience a burning sensation in the back of the throat or bitter taste during the latter part of therapy; if this occurs, interrupt therapy and have the patient drink some liquid, then resume aerosolization. The one report of hypoglycemia was mild and resolved on its own.[35] The bitter taste or burning sensation usually disappears with additional water ingestion after the therapy. Due to the demographics of the AIDS epidemic in the San Francisco area, almost all patients treated to date have been adult males, and no data are available on use in pregnant females or in children. Until definitive data are available on the teratogeny of parenteral or aerosol pentamidine, we do not recommend its use in pregnant women with PCP. Patients who are receiving aerosol therapy should be closely monitored for any of the above side effects and adverse reactions commonly seen with parenteral pentamidine. Furthermore, if pentamidine is used as therapy, clinical status must be closely followed.

Summary

Aerosolized pentamidine has been used for only 2 years for the prevention and treatment of PCP. The administration of aerosol therapy is more time-consuming and difficult than oral therapy but may prove to have fewer and less severe side effects. Although the research conducted thus far on aerosolized pentamidine for treatment and prophylaxis of PCP in patients with AIDS appears promising, we cannot recommend aerosolized pentamidine as the primary therapy for PCP until this drug is further studied. The only patients we have treated outside of prospective protocols were 12 persons who received aerosolized pentamidine for acute PCP on a compassionate basis due to intolerance to all conventional agents; fortunately, the patients all did well. However, the true utility of aerosolized pentamidine for treatment or prophylaxis of PCP can be determined only by randomized trials comparing this approach with conventional therapy. Because aerosol pentamidine is considered by the FDA to be an investigational therapy, all studies need to be conducted under an approved investigational new-drug protocol, with local institutional review board approval. We encourage other investigators to seek such approval and to conduct randomized clinical trials of this promising new therapy.

PRODUCT SOURCES

Ultrasonic nebulizers:
- Fisoneb, Fisons Corp, New Bedford MA
- Pulmosonic, DeVilbiss Health Care Worldwide, Somerset PA
- Portasonic, DeVilbiss Health Care Worldwide, Somerset PA
- "Green Machine"* by Siemens: Not available in the U.S.

Jet nebulizers:
- Fan Jet, Marquest Medical Products Inc, Englewood CO
- Respirgard II, Marquest Medical Products Inc, Englewood CO
- Aerotech II, Cadema, Middletown NY
- Centimist, Marquest Medical Products Inc, Englewood CO
- Ultra Vent, Mallinckrodt Inc, St Louis MO
- Medic-Aid System 22: Not available in the U.S.

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*"Green Machine" is a nickname, not Siemens' designation.

Air compressor:
BUNN SA 480 air compressor, The John Bunn Co, Tonawanda NY

Filter:
PALL BRO-1 filter, Pall Biomedical Products Corp, East Hills NY

Pentamidine:
Pentamidine isethionate, LyphoMed Inc, Rosemont IL

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Guidelines for Prophylaxis Against *Pneumocystis carinii* Pneumonia for Persons Infected with Human Immunodeficiency Virus

Pneumocystis carinii *pneumonia (PCP), the most common presenting manifestation of the acquired immunodeficiency syndrome (AIDS), is a major and recurring cause of morbidity and mortality for persons infected with the human immunodeficiency virus (HIV). In recent years, important advances have been made in understanding which patient subpopulations are at highest risk for developing PCP and in the design of chemotherapeutic regimens that can reduce the frequency of this illness. Recently, a number of experts* convened by the National Institutes of Health independently reviewed data on prophylaxis against PCP among persons infected with HIV, and then provided recommendations to the U.S. Public Health Service concerning which persons should receive prophylaxis and what specific prophylactic regimens should be used. The resulting guidelines are detailed below.*

BACKGROUND

Since the early 1980's, management of *PCP* has become increasingly successful, and several effective chemotherapeutic regimens are available (*1*). However, such conventional therapy as trimethoprim-sulfamethoxazole or parenteral pentamidine is often complicated by adverse reactions that may require termination of the therapy (*2*), and the mortality for first episodes of PCP is still 5%-20%. Thus, prevention of PCP is a preferred alternative to treating patients for successive episodes of this disease.

Prophylaxis against PCP is categorized as primary if the goal is to prevent an initial episode for a person who has never had PCP. Prophylaxis is categorized as secondary if the goal is to prevent subsequent episodes for a person who has already had at least one episode of PCP.

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Risk of an Initial Episode of PCP

Immunologic and clinical parameters can be helpful in determining which HIV-infected persons are at particular risk for having PCP and, therefore, which are most likely to benefit from prophylaxis against PCP. In the Multicenter AIDS Cohort Study (MACS), an ongoing prospective epidemiologic investigation of the transmission and natural history of HIV infection among homosexual men (*3*), there was a strong association ($p<0.001$) between the baseline numbers of T-helper lymphocytes (CD4+ cells) and the incidence of PCP (Table 1). Additionally, a Kaplan-Meier estimate for 323 participants whose counts of CD4+ cells were <200/mm^3 during the study showed that the proportions who had PCP by 6, 12, and 36 months were 13%, 24%, and 39%, respectively.

Similar results were seen when MACS data were analyzed by fraction of CD4+ cells expressed as a percentage of total lymphocytes rather than by absolute number of such cells. In a multivariate analysis of the prospective MACS data, thrush and persistent fever (temperature of >100°F) were additional independent predictors of the development of PCP among patients with CD4+ counts of <200/mm^{3}at their most recent evaluation (Panel of experts,* Phair and Muñoz).

A retrospective study to investigate the levels of CD4+ at which adult patients develop PCP confirms the MACS data (*4*). For the 49 episodes of PCP studied, the CD4+ counts were 1-365/mm^3 (median 26/mm^3), and the percentage of circulating lymphocytes that were CD4+ positive was 0-25% (median 4%) within 60 days before the episode (Figure 1).

Risk of Recurrent PCP

For HIV-infected persons who have had one episode of PCP, there is a high probability that a second episode will occur if no prophylactic measures are taken. Although zidovudine will reduce the frequency of second episodes (*5*), some persons who receive zidovudine have been reported to have subsequent episodes. In an ongoing study of HIV-infected patients who have had a recently documented episode of PCP (AIDS Clinical Trial Group Study 002), zidovudine therapy was started using two different dosing regimens (*6*). The study has not yet been unblinded so that

TABLE 1. Cumulative incidence* of *Pneumocystis carinii* pneumonia (PCP) according to CD4+ count at baseline among the MACS seroprevalent cohort†

CD4+ count at baseline	N	PCP	Percentage with PCP 6 mo.	12 mo.	36 mo.
≤ 200	77	19	8.4	18.4	33.3
201-350	217	47	0.5	4.0	22.9
351-500	389	39	0.0	1.4	9.0
501-700	483	43	0.0	0.4	8.3
> 700	499	20	0.0	0.0	3.8

*Kaplan-Meier estimates. Both the Logrank and Wilcoxon test statistics for differences in PCP rates by CD4+ count are statistically significant ($p<.001$)

†Participants who have taken prophylactic medication have been excluded.

investigators can determine which patients received which zidovudine regimen. A preliminary analysis was done on the risk of recurrent PCP for 318 patients followed for up to 6 months and for 122 patients followed up to 12 months on zidovudine (Figure 2) (Panel of experts,* Fischl). These results indicate a need for PCP prophylaxis in addition to antiretroviral therapy.

FIGURE 1. Most recent CD4+ enumeration (within 60 days) prior to diagnosis of *Pneumocystis carinii* pneumonia (PCP) for 49 episodes occurring among HIV-infected patients

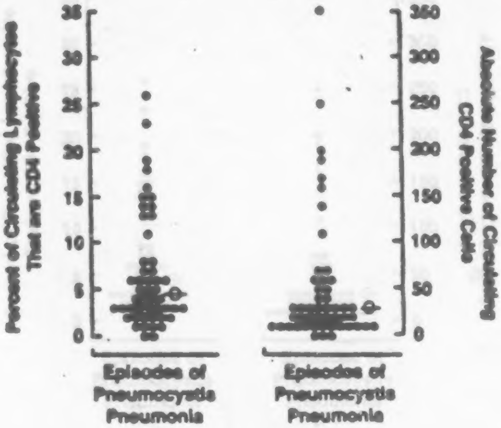
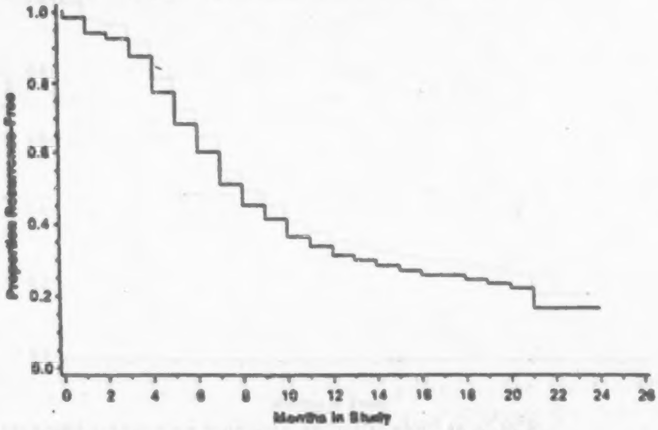


FIGURE 2. Kaplan-Meier life table probabilities of recurrent *Pneumocystis carinii* pneumonia (PCP) among patients on ACTG Protocol 002*



*All patients received zidovudine following an initial episode of PCP.

REGIMENS FOR PROPHYLAXIS

The two compounds studied most extensively for prophylaxis against PCP h been trimethoprim-sulfamethoxazole, given orally, and pentamidine, given as aerosol.

Trimethoprim-Sulfamethoxazole

The efficacy of trimethoprim-sulfamethoxazole for prophylaxis against PCP I been clearly demonstrated among pediatric cancer patients (*7-8*). The only repor randomized controlled trial of this drug combination for HIV-infected persons wa primary-prophylaxis study of 60 adult AIDS patients with Kaposi sarcoma, a compared the effect of no treatment with that of a regimen of 160 mg trimethopr plus 800 mg sulfamethoxazole twice daily plus 5 mg leucovorin calcium or daily (*9*). Compared with untreated patients, those who received prophylaxis h fewer episodes of PCP and lived longer. Adverse reactions were common (50%) a included nausea, vomiting, pruritus, and rash, although these reactions also occurr commonly among patients who were not receiving trimethoprim-sulfamethoxazc Only five patients (17%) had to discontinue prophylaxis. There are no results frc controlled trials currently available for analysis to indicate whether trimethopri sulfamethoxazole would be effective or tolerated in other populations of HIV-infect patients.

Aerosol Pentamidine

Clinical studies of aerosol pentamidine for prophylaxis against PCP have be completed by two pharmaceutical sponsors. These studies have used differe nebulizing devices and different dosing regimens.

In July 1987, a randomized, nonblinded dose-comparison study of aerosol pen midine was begun in 14 community treatment centers (*10*). The trial was open to ad patients who had already had PCP (secondary prophylaxis) as well as patients with Kaposi sarcoma and other symptomatic HIV-associated conditions who had never had PCP (primary prophylaxis). Patients were randomly assigned to three dose schedules: 30 mg every 2 weeks, 150 mg every 2 weeks, or 300 mg every 4 weeks of pentamidine delivered by the Respirgard II jet nebulizer (Marquest, Englewood, CO

An interim analysis 1 year after the start of randomization (mean follow-up of months) showed that 76 PCP episodes (13 first episodes and 63 recurrent episode had occurred: 33/135 (24%) in the 30-mg group, 25/134 (19%) in the 150-mg grou and 18/139 (13%) in the 300-mg group. For patients receiving secondary prophylax the regimen of 300 mg every 4 weeks was associated with substantially few episodes of PCP than the regimen of 30 mg every 2 weeks. There are insufficient da currently available from patients receiving primary prophylaxis to demonstra statistically significant treatment effects among the regimens.

The most common adverse effects during treatment were cough and, le frequently, wheezing—particularly among smokers and patients with a history asthma. These effects could be reduced or prevented by pretreatment with inhale bronchodilators. No systemic toxicity of the type associated with parenteral pent midine (e.g., renal insufficiency, hypoglycemia, or neutropenia) was detected, a though other reports suggest that systemic adverse effects can occur. Patien tolerated the therapy well with supervision, and only two had withdrawn because side effects at the time the interim analysis was done.

On the basis of these interim results and existing epidemiologic data from natural-history studies, the Food and Drug Administration approved a treatment IND for aerosol pentamidine as both primary and secondary prophylaxis, recommending the 300-mg dose every 4 weeks and recommending delivery via the Respirgard II jet nebulizer. The indication for primary prophylaxis in the treatment IND is a CD4+ count of <200/mm³. Secondary prophylaxis is indicated for anyone who completes therapy for an episode of PCP.

Other nebulizers have been used in trials of aerosol pentamidine prophylaxis. A double-blinded, placebo-controlled randomized multicenter trial has recently been conducted in Canada which assessed the safety and efficacy of aerosol pentamidine administered by a Fisons ultrasonic nebulizer (five 60-mg loading doses followed by biweekly doses of 60 mg). These findings have been submitted to the FDA. A study using the Fisons nebulizer and three different doses of aerosol pentamidine ~~has~~ also been completed in the United States and is currently being evaluated.

RECOMMENDATIONS

On the basis of the data summarized above and the opinions of individual members of the panel of experts, the Public Health Service recommends that—unless contraindications exist—physicians should initiate prophylaxis against PCP for any HIV-infected adult patient who has already had an episode of PCP, even if the patient has been receiving zidovudine. Unless contraindicated, prophylaxis should also be initiated for HIV-infected patients who have never had an episode of PCP if their CD4+ cell count is <200/mm³ or if their CD4+ cells are <20% of total lymphocytes. Patients with CD4+ cell counts of <100/mm³ or CD4+ cells <10% and patients with oral thrush or persistent fever (temperature of >100°F) are at particularly high risk for PCP.

Patient Evaluation

For HIV-infected persons, CD4+ lymphocyte percentages or counts should be monitored at least every 6 months. Some experts prefer to obtain a second count within a few months of the first count to assess the rate of decline. Subsequent CD4+ enumerations may be desirable at intervals of <6 months in certain situations such as: a) the presence of fever or thrush, b) a recent rapid decline in CD4+ cell count, c) a CD4+ percentage in the 20-30 range, or d) a CD4+ absolute number in the 200-300/mm³ range. If a decision to start prophylaxis is to be made on the basis of a low CD4+ cell count or percentage, the CD4+ enumeration should probably be repeated, unless previous determinations indicate the low count or percentage is consistent with an established trend.

Some patients may have discordant CD4+ percentages and absolute counts, i.e., the percentage may be >20% while the CD4+ count may be <200/mm³, or vice versa. In such cases, it is probably prudent—after reconfirming the CD4+ enumerations—to assume that the patient is at high risk for PCP if either of these two parameters is in the high-risk range.

Clinicians should be aware that in certain unusual circumstances, either the absolute CD4+ count or the CD4+ percentage may not be an accurate reflection of [illegible] PCP. For example, after splenectomy, HIV-infected patients may be susceptible despite normal CD4+ counts. Conversely, some laboratory reagents may not detect CD4+ markers on the T-helper cells of all persons (*11*), so that such persons may speciously appear to be in the susceptible range. In situations in which this phenomenon is suspected (e.g., when the sum of the number of CD4+ cells and CD8+ cells does not approximately equal the number of CD3+ cells), the lymphocyte sample should be retested with other CD4+ reagents.

Before prophylaxis against PCP is administered, patients must be evaluated to exclude certain active pulmonary diseases. If symptoms, signs, or radiologic abnormalities suggest that active disease is present, a thorough evaluation for community-acquired pathogens (e.g., *Pneumococcus*), opportunistic pathogens (e.g., *Pneumocystis*, cytomegalovirus), communicable pathogens (e.g., *Mycobacterium tuberculosis*), tumors, or other processes is indicated. As with other HIV-infected persons, these patients should be given a Mantoux skin test with 5-TU tuberculin, PPD (*12*).

Choice of Prophylactic Agent

Scientific studies available to date suggest the following two approaches are effective and safe, although neither has been approved as labelling indications by the Food and Drug Administration.

1) Although it has been studied less extensively among HIV-infected persons than aerosol pentamindine, oral trimethoprim-sulfamethoxazole (160 mg trimethoprim and 800 mg of sulfamethoxazole) can be given twice daily with 5 mg leucovorin once daily. This form of prophylaxis should not be given to patients with a history of type-I hypersensitivity (angioedema or anaphylaxis) or prior episodes of Stevens-Johnson syndrome associated with sulfonamides or trimethoprim. The efficacy of leucovorin in prevention of toxicity is unknown.
2) Aerosol pentamidine can be given as 300 mg every 4 weeks via the Respirgard II jet nebulizer. The dose should be diluted in 6 ml of sterile water and delivered at 6 liters/minute from a 50-PSI compressed air source until the reservoir is dry. (Further information can be obtained by telephoning the Treatment IND number: 1-800-727-7003.) Because other doses and aerosol delivery systems have not yet been adequately studied and analyzed, no recommendations regarding such systems can be made. For patients who develop cough or wheezing while receiving aerosol pentamidine, pretreatment with a bronchodilator can be tried before the aerosol therapy is given again. Patients with asthma or an extensive history of smoking may not tolerate this form of therapy, and it may not be prudent treatment for a patient with a prior life-threatening reaction to parenteral pentamidine.

Since neither aerosol pentamidine nor oral trimethoprim-sulfamethoxazole prophylaxis is known to be safe in association with pregnancy, it is inadvisable to give either agent to HIV-infected pregnant women. Rather, such women should be monitored carefully for symptoms, signs, or laboratory abnormalities suggestive of PCP. Prophylaxis can then be considered for use in the postpartum period. Careful monitoring is also indicated for patients intolerant of aerosol pentamidine and trimethoprim-sulfamethoxazole, or for those unwilling to receive prophylaxis.

Alternative regimens that are of unproven efficacy and safety for humans, but that might be considered for prophylaxis, include dapsone (daily or weekly), dapsone plus trimethoprim (daily or weekly), or dapsone plus pyrimethamine (daily or weekly) and pyrimethamine-sulfadoxine (weekly).

Follow-Up of Patients Receiving Prophylaxis

Since none of the regimens has been shown to be completely protective against PCP for HIV-infected persons, patients who receive prophylaxis should be monitored closely for evidence of PCP, as well as other pulmonary infections. If prophylaxis is discontinued, the patient will again be at increased risk for developing PCP.

Prophylaxis failures have been reported in which persons given aerosol pentamidine, especially at low doses, later had PCP in the upper lobes of the lung (13). In addition, prophylaxis using aerosol pentamidine does not offer protection against extrapulmonary pneumocystosis (14).

Prophylaxis for Infants and Children

Pneumocystis carinii pneumonia is a common manifestation of pediatric AIDS. Most experts agree that some form of prophylaxis is warranted for HIV-infected pediatric patients who are at high risk for PCP on the basis of criteria that are analagous to those described above for adults. However, there are insufficient data about the efficacy or toxicity of prophylactic regimens for pediatric patients, so that no scientifically validated guidelines can be provided as yet. There are no data concerning the appropriate dose or delivery system of aerosol pentamidine for infants or children. The appropriate dose of trimethoprim-sulfamethoxazole prophylaxis might be estimated from trials involving pediatric cancer patients (e.g., trimethoprim 75 mg/M^2 plus sulfamethoxazole 375 mg/M^2 given orally every 12 hours) (*7,8*).

Further Information

Several studies are under way to gain additional information about prophylaxis against PCP. Information about these studies can be obtained from the National Institute of Allergy and Infectious Diseases Information Office (1-800-TRIALS-A) or the American Foundation for AIDS Research (212-333-3118).

EDITORIAL COMMENTARY

These guidelines for prophylaxis against PCP indicate a medical benefit from the careful clinical and immunologic monitoring of persons infected with HIV and have several important implications. First, the guidelines are likely to increase the demand for HIV antibody testing by persons who believe they may be at risk for infection. The Public Health Service has estimated that between 945,000 and 1.4 million persons in the United States are infected with HIV (*15*). Of these persons, CDC estimates that approximately 120,000 have been informed of their infection status as a result of voluntary antibody testing carried out in public (primarily Federally funded) HIV counseling and testing centers. The number of persons found through other sources of testing to be infected is unknown, but it is likely that many persons who are infected are not aware of their infection. Persons at risk who have not had HIV antibody testing should now consider such testing because they may be candidates for prophylaxis against PCP if they are found to be infected.

Second, the guidelines are likely to increase the demand for medical services by asymptomatic HIV-infected persons. Such persons will need medical evaluation to determine whether they are candidates for prophylaxis against PCP, and—if prophylaxis is given—these persons will need medical follow-up. All persons found to be infected at HIV counseling and testing centers should be referred for further medical evaluation, including a measurement of their CD4+ cells. Facilities offering HIV counseling and testing should develop referral networks of medical-care providers sufficient to evaluate and care for the infected persons they identify. These networks should include services related to family planning and treatment for intravenous drug addiction, sexually transmitted disease, and tuberculosis.

Third, the guidelines are likely to increase the demand for flow-cytometry services to quantify CD4+ cells from HIV-infected persons. Laboratories to which samples are referred for flow cytometry should have prior experience, since methodology can greatly influence the quality of test results. Although there are no true reference standards for evaluating blood cells, quality can be assured by adhering to criteria that address sample collection, preparation, instrument calibration and standardization, flow cytometric analysis, and adequate training of operators (*16*). Either absolute CD4+ counts or percentage CD4+ cells can be used in monitoring HIV-infected persons. There appears to be less day-to-day fluctuation in percentage of CD4+ cells compared with absolute number, suggesting that the former measure may be more reliable (*4,17*). This finding is not unexpected since the percentage of CD4+ cells is directly measured by flow cytometry, whereas the absolute number is calculated from the absolute and differential white-blood-cell count and the percentage of CD4+ cells.

Fourth, health-care providers who administer aerosol pentamidine as prophylaxis against PCP should be aware of several occupational safety issues. In particular, they should note the recommendation to exclude active pulmonary disease before starting prophylaxis. A recent investigation of *M. tuberculosis* infections among the staff members of a health clinic in Florida suggested that one source of infection may have related to the use of aerosol pentamidine treatment for two patients who had positive sputum cultures for *M. tuberculosis* during the time they received aerosol pentamidine. One of these two patients coughed profusely both during and after therapy (*18*). Providers administering aerosol pentamidine should also review the manufacturer's instructions for the use of the nebulizer system. The Respirgard II nebulizer contains a filter designed to remove most of the pentamidine from exhaled gases. If the nebulizer is improperly used, substantial amounts of pentamidine can be released into the environment, and health-care workers or others in the vicinity may be at risk for the same adverse events as the patients who received the therapy (*19*).

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Pneumocystis carinii Pneumonia in Patients With the Acquired Immunodeficiency Syndrome: Pathophysiology, Therapy, and Prevention

A. Bruce Montgomery

The continuing growth of the acquired immunodeficiency syndrome (AIDS) epidemic has caused a parallel increase in patients with *Pneumocystis carinii* pneumonia (PCP). PCP has a wide spectrum of severity, from mild disease to severe parenchymal lung damage. Outcome is determined by severity of lung injury, the underlying physical condition of the patient, and concomitant infections. Both trimethoprim-sulfamethoxazole (TMP-SMX) and pentamidine are effective therapeutic agents; however, both cause a high incidence of adverse reactions. TMP-SMX therapy can be made safer by careful monitoring and dose adjustment. Pentamidine toxicity, especially hypoglycemia, appears to be cumulative dose-dependent. Experimental therapies, including TMP-dapsone and aerosolized pentamidine, appear promising in mild to moderate disease, while trimetrexate may be more effective in severe disease. Corticosteroids are unproven in decreasing mortality. Prophylaxis of PCP is possible with TMP-SMX but the high rate of adverse reactions make long-term therapy difficult. Other oral therapies such as dapsone, pyrimethamine/sulfadoxine are also promising but not yet tested. Aerosolized pentamidine is effective and safe for prophylaxis regimen when administered correctly. Airway irritation as manifested by cough and/or wheezing is a common adverse effect of aerosolized pentamidine.

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THE EXPLOSIVE GROWTH of the acquired immunodeficiency syndrome (AIDS) epidemic has been paralleled by the current and projected future case load of patients with *Pneumocystis carinii* pneumonia (PCP). In the United States alone, over 35,000 AIDS patients with PCP were treated in 1988. In spite of this plethora of clinical material, the paucity of completed, well-designed clinical trials has led to considerable controversy in optimal therapy and prophylaxis. In this chapter I intend to clarify the pathophysiological basis of PCP, and to review treatment and prophylaxis, including investigational therapies.

PATHOPHYSIOLOGY OF PCP

P carinii, although currently classified as a protozoan may well be a fastidious fungus.[1] No environmental saprophytic form has been described. Asymptomatic primary infection from *P carinii* presumably occurs in childhood, while pneumonia occurs from reactivation of dormant organisms in the setting of immunosuppression. However, focal epidemics of pneumonia reported among immunosuppressed patients have suggested airborne infection. The degree of immunosuppression in AIDS patients may be quantified by the CD4 (or T-helper) lymphocyte count, which normally is >1,000 cells/mm^3. PCP usually occurs in patients with absolute CD4 counts of <200 cells/mm^3, although the disease can occur in patients with CD4 counts of >500 cells/mm^3, especially if they have received concomitant chemotherapy.[2,3]

P carinii parasitizes the surface of the alveolar epithelial cells. The small trophozoites develop into cysts and produce daughter trophozoites that are then released when the cysts burst.[4] Progressive infection, occurring over days to weeks, usually results in a diffuse alveolar filling process that causes progressive dyspnea, hypoxemia, and an reticulonodular pattern on the chest radiograph.[5] The degree of severity of altered gas exchange is roughly correlated with survival: a partial pressure of oxygen in arterial blood (PaO_2) of less than 50 torr on admission in patients' breathing room air is associated with 30% to 40% mortality, whereas the mortality is 5% to 10% among patients whose PaO_2 is greater than 70 torr on ambient air on presentation.[6,7]

Large numbers of *P carinii* increase the permeability of the alveolar capillary membrane.[8,9] The physiologic consequence of increased alveolar capillary permeability is a form of the adult respiratory distress syndrome (ARDS) with loss of surfactant, leading to noncompliant, stiff lungs, and high mortality in the face of therapy with

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mechanical ventilation with positive end-expiratory pressure (PEEP). This is a severe form of ARDS and antimicrobial therapy may not be the major determinant of outcome in the presence of such severe parenchymal lung injury.

Extrapulmonary infection with *P carinii* is rare; the incidence appears to be less than one case report for every three thousand AIDS patients with PCP. The mechanism of extrapulmonary spread is not known. Local spread may occur via the lymphatic system, whereas disease in the ear canals and gastrointestinal (GI) tract implies passage through the airways or gut. On the other hand, infection in the retina and adrenals suggest blood-borne spread. The manifestations of extrapulmonary pneumocystosis are often occult, and the significance of this condition in terms of patient survival is unclear.

STANDARD THERAPY

The only therapies currently approved by the Food and Drug Administration for treatment of PCP are trimethoprim-sulfamethoxazole (TMP-SMX) and pentamidine.[10-14] TMP-SMX is the prototype agent of purine synthesis inhibition and blocks folate metabolism at two sites, dihydrofolate reductase inhibition and a synergistic inhibition of dihydrofolic synthetase. TMP has at least a 2,000-fold greater affinity for microbial than mammalian dihydrofolate reductase.[12] SMX interferes with dihydrofolic synthetase, a enzyme found only in microbes that convert para-aminobenzoic acid to dihydrofolic acid.

TMP and SMX are well suited for combination therapy because they also have a broad range of antimicrobial activity, are well absorbed after oral administration, and have similar peak concentrations and half lives. Peak serum levels of both agents occur within one to three hours; the serum half-life is 12 to 13 hours. Unfortunately, TMP and SMX are chemically incompatible in most solutions and therefore require dilution. Even if TMP-SMX solutions are double concentrated, at least 1 L of free water is administered daily to the average patient, which may cause fluid overload and hyponatremia.

The standard dose of TMP/SMX used for PCP is 15 to 20 mg/kg/d TMP with 75 to 100 mg/kg/d SMX given either intravenously (IV) or orally at six-hour intervals.[10,15] Although the upper range dose has been recommended in patients with AIDS,[7,8] recent studies have demonstrated that AIDS patients may be treated at the lower range with equal efficacy. In addition, adverse reactions such as neutropenia can be ameliorated by TMP dose adjustment.[15] Although the optimal duration of treatment for PCP in AIDS patients in not known, TMP-SMX is usually given for 14 to 21 days. TMP-SMX was used extensively in children and adults with PCP before the AIDS epidemic, with low reported rates of toxicity. However, a wide spectrum and severity of adverse reactions has been reported in AIDS patients.[10,15,16] Forty to 60 percent of AIDS patients with PCP are unable to complete a therapeutic course with TMP-SMX because of adverse reactions, and most other patients experience milder degrees of toxicity.[10,16] Common adverse reactions mandating a change of therapy include a rash with exfoliation or mucositis, severe neutropenia, thrombocytopenia, and chemical hepatitis.[10,16] Common adverse reactions that mandate close observation and daily laboratory evaluation include lesser degrees of the above reactions as well as nausea, vomiting, and hyponatremia.

Pentamidine is an aromatic diamidine that was initially synthesized in the 1930s in a search for hypoglycemic agents. Because of its antiprotozoal activity, pentamidine has been used extensively for treatment and chemoprophylaxis of African trypanosomiasis. The exact mechanism of action of pentamidine is not known; in vitro it interferes with folate metabolism, anaerobic glycolysis, oxidative phosphorylation, and nucleic acid replication.[11] Peak serum levels of pentamidine occur within one hour after parenteral administration; elimination half-life occurs between six and ten hours. Pentamidine has a large apparent volume of distribution due to avid tissue uptake.[13] The tissue half-life of pentamidine is more than 30 days in the lungs and other tissues.[13,14]

Pentamidine usually is given parenterally in a dose of 4 mg/kg/d as the isethionate salt, the only preparation available in the United States.[11] Parenteral administration is necessary because GI absorption is poor. The drug is best administered IV over a period of 60 to 90 minutes in 250 mL of 5% dextrose to minimize dose-related hypotension. Intramuscular (IM) administration is not favored due to a high incidence of sterile abscesses at the injection sites. As with TMP-SMX, the optimal duration of PCP therapy for PCP in AIDS patients is not known. Nevertheless, 14 to 21 day courses are standard and longer courses may be needed in patients with a slow clinical response.

Unfortunately, as occurs with TMP-SMX at standard doses, many patients given pentamidine for more than 1 week experience adverse reactions, 40% to 50% of which are severe enough to require change of therapy.[10,11,17] Adverse reactions to pentamidine appear to be dependent in part on the cumulative dose. A 3-g total dose, which is usually reached in the second week of parenteral therapy, is likely to cause toxicity.[17] The most common adverse reactions are azotemia, hypoglycemia, and neutropenia, the last of which is rarely seen in non-AIDS patients. Other reported reactions include chemical hepatitis, nausea with vomiting, hypocalemia, and cardiac arrhythmias.[10,11,17] Hypoglycemia may result from pentamidine-induced damage to beta cells in the pancreas and has been followed by the development of diabetes mellitus.[17] Cardiac arrhythmias are rare but are difficult to manage due to the long tissue half-life of pentamidine.

The management of adverse reactions requires both anticipation and response. Complete blood counts, and tests of hepatic and renal function are needed at initiation of therapy, and every three days thereafter. Adverse reactions requiring change of therapy commonly include exfoliative rash or mucositis, neutropenia, thrombocytopenia, and altered renal or liver function. However, clinicians vary on the acceptable degree of severity.[10,11,15-17] If parenteral pentamidine is used, blood glucose and blood pressure should be monitored, usually in a supervised clinical setting.[17]

If a significant adverse reaction develops to either TMP-SMX or parenteral pentamidine, patients can be switched to the other agent. There are several possible options for patients intolerant to both TMP-SMX and parenteral pentamidine. Rechallenge with TMP-SMX may be worthwhile, especially in situations in which other drugs may have caused or contributed to the adverse reaction. Rechallenge may be helpful if neutropenia occurred during initial treatment because the neutropenia as noted with TMP probably is dose-related.[15] However, this approach would not be advisable in patients with a past history of severe exfoliative rash with mucositis. Treatment with the experimental antimicrobials noted later is another option, although the comparative efficacy of these approaches in patients who are severely ill is not known. Another alternative is to discontinue all drugs if 14 days of therapy has been administered and an adequate clinical response obtained.

The frequent need to change therapy has made it difficult to determine the true efficacy of TMP-SMX and pentamidine or both in AIDS patients with PCP (Table 1). Of particular interest are the discordant findings in the studies by Wharton et al[10] and Sattler et al.[15] The former study showed 75% survival in patients randomized to receive TMP-SMX and 95% survival in those randomized to pentamidine, whereas the latter trial had 86% survival in the patients receiving TMP-SMX and 61% in the patients receiving pentamidine. Neither trial was blinded, which probably is of little consequence when an endpoint such as death is used. Random chance may have favored pentamidine in the Wharton et al trial, which included only 40 patients; Sattler et al entered a greater number of patients, who had second episodes of PCP, in the pentamidine arm. The variability of mortality data in these studies also suggests that severity of respiratory

Table 1. TMP/SMX and Pentamidine for PCP in AIDS

Reference	Study Type	N	Agent	ADR Requiring Drug Change (%)	Failures (%)	Salvage With Other Drug (%)	Deaths (%)
Murray et al[16]	Historic	186	TMP/SMX	22	30	11	28
Wharton et al[10]	Prospective	20	TMP/SMX	80	25	0	25
	Trial	20	PTN	55	5	0	05
Sattler et al[15]	Prospective	36	TMP/SMX	0	14	0	14
	Non-cross-over with dose adjustments	34	PTN	3	39	0	39

Abbreviations: ADR, Adverse drug reaction; TMP/SMX, trimethoprim sulfamethoxazole; PTN, Pentamidine.

failure, concomitant diseases, and nutritional status also determine mortality. This is underscored by the fact that salvage after initial treatment failure is usually unsuccessful regardless of antimicrobial agent (Table 1).[11,15,18]

Response to therapy, judged by degree of respiratory failure, fever, and chest radiographs is often slow, and many patients continue to deteriorate clinically for several days after treatment is started regardless of which antimicrobial agents are administered.[11,15] A period of at least four to six days is therefore required before determination of drug failure. Fever, hypoxemia, and dyspnea should be resolved and radiographic improvement should be apparent within 14 to 21 days of treatment. The use of bronchoscopy to assess response is not useful because many patients have persistent organisms in respiratory secretions despite clinical improvement.[19] The viability of these persistent organisms is not known because no clinically available stain can distinguish live from dead organisms. It is worthwhile to obtain chest radiographs and pulmonary function tests 1 month after therapy to provide a new baseline should questions of recrudescence occur.

EXPERIMENTAL THERAPY

Pentamidine can be delivered directly to the lungs by aerosolization.[20-23] Because *P carinii* organisms are almost exclusively intra-alveolar, aerosolized pentamidine with alveolar targeting and binding and low systemic absorption should be as effective and less toxic than parenteral pentamidine.[20-23] The most important factor in giving aerosolized pentamidine probably is the choice of nebulizer. The optimal particle size for alveolar deposition is between 1 to 2 μm with 1 μm achieving more peripheral and less central airway distribution. Therefore, a nebulizer generating 1 to 2 μm particles with a high output would appear to be ideal.[20] Devices with a reservoir may increase delivery as the drug concentration on the first part of inspiration is more important than the average concentration; this is because the initial volume inspired will be more peripherally distributed. Many patient factors also affect aerosol deposition, including the rate of inspiratory flow, tidal volume, variations of airway geometry, and presence of other pathological processes.[20]

Four pilot studies using aerosolized pentamidine have been conducted (Table 2).[21-24] Montgomery et al[22] studied one group of AIDS patients with PCP who had received no prior therapy[22] and a second group that was intolerant to standard therapy.[23] Of the 25 patients treated, 23 recovered. Relapses occurred in only three patients during a mean follow-up period of over 1 year. No adverse systemic reactions were observed during aerosolized pentamidine in either group; coughing was noted in patients with a history of bronchospasm or smoking. This was treated successfully with an aerosolized bronchodilator.[22] Conte et al[23] also studied the effects of inhaled or reduced-dose pentamidine treatment of PCP in AIDS patients. Nine of the 13 patients with mild PCP had a satisfactory response to inhaled aerosolized pentamidine; three patients could not be evaluated due to early withdrawal and one patient had treatment failure. Two of the nine evaluable patients had neutropenia, but those patients had been receiving zidovudine (AZT) (Burroughs Wellcome Co, Research Triangle Park, NC) and had low pretreatment leukocyte counts. Other mild adverse reactions included cough, bronchospasm, rash, and elevated temperatures. The fourth study was done by Miller and Semple[24] who initially reported little success with aerosolized pentamidine using one type of nebulizer, but had better

Table 2. Aerosolized Pentamidine Studies for Mild to Moderate PCP in Patients With AIDS

Reference	Study Group	N	Nebulizer Type	ADR Requiring Drug Change (%)	Failures (%)	Deaths (%)
Montgomery et al[21]	First episode	15	Respirgard II	0	14	7
Montgomery et al[22]	Intolerant to other agents	10	Respirgard II	0	0	0
Conte et al[23]	Mixed	13	Ultravent	0	31	0
Miller and Semple[24]	Mixed	11	System 22	9	72	9
	Mixed	16	Respirgard II	0	19	0

results using a nebulizer that generated smaller particles. These results highlight the importance of aerosol particle size and the need for large, randomized trials before aerosolized pentamidine can be accepted as standard therapy.

Trimethoprim-dapsone (TMP-DAP), another antifolate combination that inhibits purine synthesis, has been shown to be effective therapy for PCP in animal models, in an open pilot study, and in a double-blind comparison to TMP-SMX.[25,26] The pharmacokinetics of this combination appear to be unique in that each drug interferes with the other's metabolism so the optimal dosage regimen is not known. In both clinical studies, only patients with mild to moderate PCP were studied, in part because there is no IV preparation of dapsone.[25,26] In the open study, 13 of 15 patients responded to TMP-DAP; in the double-blind study, 28 of 30 patients responded compared with 27 of 30 taking oral TMP-SMX (20 mg/kg/d TMP and 100 mg/kg/d SMX). All patients failing to respond to oral TMP-DAP or TMP-SMX responded to standard IV therapy with pentamidine or TMP-SMX.

Severe adverse reactions occurred in two of 15 patients in the open pilot study. In the blinded study, nine of 30 patients taking TMP-DAP had severe reactions compared with 16 of 30 taking TMP-SMX. Regardless of therapy, almost all patients had mild to severe nausea, vomiting, or both. In the open study, TMP dosage was often decreased because of mild rashes, a factor that may have ameliorated some of the toxicity seen in the blinded study. Other adverse reactions reported with TMP-DAP, some severe enough to require discontinuation of therapy, included hyperkalemia, methemoglobinemia (unique to dapsone), elevated liver enzymes, neutropenia, and thrombocytopenia.

Trimetrexate, unlike trimethoprim, is a potent inhibitor of both mammalian and protozoal dihydrofolate reductase.[12] This agent easily enters both the pneumocyst and mammalian cells due to its lipid solubility. Folinic acid (leukovorin) must be administered as a specific antidote to protect host tissues from toxic antifolate effects. Folinic acid, which is not lipid soluble, is actively transported into mammalian but not into *P carinii* cells.

Preliminary studies with trimetrexate, leukovorin, and sulfadiazine reveal responses and adverse reactions similar to those with TMP-SMX.[27] Particularly promising results were seen in patients receiving salvage therapy after failing to respond to standard therapy. Eleven of 16 patients survived, a considerable improvement compared with what has been reported in similar patients in other studies.[10] Trimetrexate with leukovorin alone appears to be as effective as TMP-SMX and to have fewer adverse reactions. Therefore, this formulation is under active study because it would have a definite advantage over standard therapy. However, a significant relapse rate of PCP occurs within 6 weeks of ending therapy, and current studies are adding a secondary prophylaxis arm.[27]

Dimethylfluoronithine (DFMO) inhibits orthinine decarboxylase and therefore interfere with protein synthesis. This agent has been shown to be variably effective in treating rats with PCP. In humans, McLees et al[28] reported on salvage therapy with DFMO in 234 patients after treatment failure with standard agents. Short-term mortality was high, but 84 of 234 (36%) patients survived. The most common adverse reaction noted was thrombocytopenia. To date, DFMO has not been specifically tested in a large trial without the prior administration of other antimicrobials; a synergistic or residual effect from tissue-bound pentamidine is possible.

ADJUNCTIVE THERAPY

Three forms of adjunctive therapy–corticosteroids, positive pressure breathing, and nutrition–are currently advocated for use in AIDS patients with PCP. Putative mechanisms for a beneficial action of corticosteroids include suppression of inflammatory cell influx into the lung, decreasing interstitial edema, and stabilization of alveolar capillary membranes. MacFadden et al[29] reported a dramatic reversal of respiratory failure with high-dose corticosteroids in ten patients. Despite this response, however, it should be noted that corticosteroids do not improve the outcome of ARDS due to causes other than PCP and may be harmful.[30] Possible side effects include secondary viral pneumonias, especially due to cytomegalovirus, or the development of other nonpulmonary opportunistic infections from increased immunosuppression. Furthermore, the increased survival in corticosteroid-treated patients may reflect other improvements in patient care or early diagnosis.

In a prospective double-blind, placebo-controlled trial in which 60 mg IV methylprednisolone was given every four hours for 48 hours with subsequent taper no statistically increased survival in AIDS patients with severe PCP was seen.[31] Due to the moderate sample size, corticosteroids cannot be said to be without any possible benefit. Nevertheless, this study established that placebo-controled trials are ethical and should prompt larger trials.

Good nutrition is often difficult to provide consistently in AIDS patients. In both animal models and in pediatric patients, starvation appears to be a major cofactor in the onset and outcome of PCP. Indeed, serum albumin concentrations of <2.0 g/dL are common in patients with severe PCP. Considering the long time required to recover from a severe episode of PCP, early consideration of enteral hyperalimentation may be appropriate. However, AIDS patients often selectively malabsorb fat emulsions that are the major components of many tube feedings and supplemental diets. Therefore, a high carbohydrate diet is probably superior in such patients. Alternatively, parenteral hyperalimentation is sometimes needed.

Oxygen is an important adjunctive therapy in PCP. Unfortunately, the high concentrations of oxygen required for some patients cannot be provided with standard tightly fitting reservoir face masks. One option is continuous positive airway pressure that provides not only a high oxygen concentration but also positive airway pressure that additionally improves oxygenation. The drawback to this approach is that the masks are uncomfortable to wear and may cause nasal bridge pressure necrosis. Another, easily tolerated approach is giving a high flow of oxygen at 50 L/min and using rebreathing whiskers with a standard face mask. Patients who cannot be oxygenated by these methods usually require intubation and mechanical ventilation.

PROPHYLAXIS

Continued exponential growth in the incidence of PCP is expected, unless effective prophylaxis for this disease is developed and implemented. In 1990 alone, 40,000 to 60,000 cases of first-episode PCP are expected in the United States as noted earlier. Furthermore, the annual number of repeat PCP episodes from AIDS patients surviving from prior years will increase this total by 30%. The mortality for each occurrence is 10% to 30% in patients ill enough to be hospitalized.[32]

The risks of recurrent PCP have been assessed by historical studies and in ongoing clinical trials of zidovudine. Analysis of 201 consecutive patients with first-episode PCP at San Francisco General Hospital has shown that 61 (30%) relapsed with PCP. The cumulative of incidence relapse in survivors was 18% at 6 months, 46% at 9 months, and 65% at 18 months.[32] Most patients with a second episode of PCP are expected to relapse within 18 months. The above data were collected prior to the introduction of zidovudine when competing mortality limited the absolute numbers of second-episode PCP. Although zidovudine decreases primary PCP,[33] comparison of the relapse rates of PCP before and after zidovudine became available suggests that, although the risk of PCP may be slightly decreased in individual patients, overall risk is increased because patients live longer with AIDS.[34]

Unblinded or uncontrolled trials of various therapeutic regimens including oral TMP-SMX, oral pyrimethamine sulfadoxine, oral dapsone, and parenteral pentamidine in AIDS patients have been reported to decrease the recurrence of PCP compared with historical or concurrent controls.[35-39] A common finding in all studies is that primary prevention trial require larger number of patients due to the lower incidence of PCP in this group compared with that observed during prophylaxis following an episode of PCP.

TMP-SMX provides effective prophylaxis when given twice daily every day and three days per week in children with hematological malignancies who were receiving chemotherapy.[40,41] The children on the three-times-a-week regimen had a lower incidence of systemic fungal infections but other toxicity was similar. Previous investigators have had difficulty in administering chronic TMP-SMX to patients with AIDS and AIDS related complex (ARC) because of dose-limiting toxicity including nausea, vomiting, rash, fever, or marrow suppression.[39] Nevertheless, a regimen consisting of twice daily TMP-SMX double-strength tablets with 5 mg folinic acid was recently shown to provide effective primary prophylaxis for Kaposi's sarcoma patients undergoing chemotherapy.[3] Fifty percent of these patients suffered minor toxicity and 17% suffered dose-limiting toxicity. The investigators continued treatment despite the development of skin rash, a condition that prompts most physicians to discontinue the drug. Whether this regimen would be beneficial to AIDS patients receiving zidovudine is difficult to assess, given the possibility of bone marrow suppression from both agents.[10,42] Furthermore patients requiring secondary prophylaxis may have been sensitized to sulfa agents during their treatment for PCP and may therefore manifest greater toxicity.[10]

Another antifolate combination, 25mg pyrimethamine plus 500 mg sulfadoxine has been administered once a week to a group of patients.[36] After a mean follow-up time of 11 months (range: 3 to 27 months) only five of the 60 patients in this study experienced a second episode of PCP. In six patients, pyrimethamine sulfadoxine was discontinued because of rash. Anecdotal reports of lack of clinical efficacy and of the development of Stevens-Johnson syndrome in several patients have discouraged prospective trials of this agent.[37] In addition, as an antifolate, pyrimethamine sulfadoxine could also cause additive or synergistic marrow suppression with zidovudine.

Parenteral pentamidine has also been given prophylactically in 4 mg/kg doses once a month. This approach appears promising, but toxicity should be expected after a cumulative dose of 3 g as noted earlier.[17] Another potential prophylactic agent is dapsone, a sulfone.[38] The efficacy of dapsone as secondary prophylaxis of PCP in a controlled trial has not been reported. Because the incidence of toxicity in AIDS patients receiving high-dose dapsone therapy for PCP are well known, it must be determined whether low or intermittent dosage can provide effective prophylaxis with acceptable levels of adverse reactions, especially anemia.

Aerosolized pentamidine is also a promising regimen for prevention of PCP in AIDS patients.[39] In the largest study of this agent to date, Leoung et al[43] followed 439 patients with either prior PCP (n = 250), Kaposi's Sarcoma (n = 59), or ARC (n = 129). Patients were randomized to receive either 30, 150, or 300 mg of aerosolized pentamidine using the Respirgard II Nebulizer System. The 30 and 150 mg doses were administered every 2 weeks; the 300-mg dose was given every 4 weeks. The once monthly 300-mg regimen was superior to the 30-mg regimen ($P < .001$) in that only 13 episodes of PCP were observed in the patients receiving the former regimen compared with 27 patients receiving the latter over a mean follow-up time approaching 1 year. The once monthly regimen also tended to be more superior than the 150-mg regimen (Dave Feigal, personal communication). The absolute benefit of aerosolized pentamidine in secondary prophylaxis will never be known because the apparent benefits of the aerosol probably will preclude placebo studies. Nevertheless, based on a recurrence rate of up to 60% per year in historical controls, the relative protection from aerosolized pentamidine may be as high as tenfold.

Aerosolized pentamidine does not provide perfect prophylaxis; however, most cases of relapse are mild with a case fatality rate of <5%. Lowery et al[44] reviewed the radiographic pattern of relapse in patients on low-dose aerosolized pentamidine and found a striking increase of upper lobe relapses, an observation that correlates with the predicted deposition of most of the drug in the better-ventilated, lower lobes.[44] The best breathing patterns would be those that encourage apical deposition such as exhalation to residual volume followed by full inspiration or changing positions. Breath holding at increased lung volumes that decreases apical deposition would not be useful.

The use of aerosolized pentamidine in primary prophylaxis is logical based on the above data if a high-risk population can be identified. As noted before, a CD4 cell count of <200 cells/mm³ was present in most patients with PCP 2 months prior to their initial episode.[3] As CD4 counts have some inherent variability and are expensive to check frequently, institution of prophylaxis is probably appropriate at levels somewhat above 200 cells/mm³. Because the long-term consequences of aerosolized pentamidine prophylaxis are not known, administering the drug to patients at low risk (CD4 above 500 cells/mm³ and no other immunosuppressive therapy) is not warranted.

Systemic side effects of aerosolized pentamidine reported to date occur at a frequency of <1% and include mild hypoglycemia, extrapulmonary pneumocystosis, and eosinophilic pneumonia.[20] Airway irritation with cough (10% to 20%) or bronchospasm (1% to 2%) occurs commonly. This may be due to either the isethionate with the SO_3 moiety or the pentamidine base.[20] The cough apparently responds or can be prevented with inhaled bronchodilators.[20] The long-term administration does not appear to cause permanent airflow obstruction or a reduction in diffusing capacity. Airway deposition and hence airways toxicity can be minimized by nebulizer choice.[20] Aerosolized pentamidine does not appear to cause additive or synergistic toxicity to zidovudine. Pneumothoraces have been reported in patients on aerosol pentamidine prophylaxis. However, the incidence appears less than what was reported in patients without prophylaxis after PCP.

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APPENDIX 7

ADDITIONAL INFORMATION FROM PARTNERS NATIONAL HEALTH PLANS

PARTNERS
National Health Plans

Drug Update

JANUARY 1989

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ADVERSE DRUG EVENT (ADE) REPORTING

With the increased interest in the medical community about outcomes of care, the ADE reporting system of the FDA has assumed more importance as a possible tool. ~~Collection and analysis~~ of ADE reports could 1) provide early warnings of previously undetected, serious drug risks, 2) directly change recommendations for a drug's use, 3) help profile types of reactions occuring for a group of drugs or 4) provide information on patient risk factors. What is a "serious" ADE? To date, the FDA defines a serious ADE as an event that is associated with one or more of the following: death, new or prolonged hospitalization,permanent or severe disability, congenital anomaly, cancer or overdose. By law, all physicians are required to report serious vaccine or toxoid ADEs directly to the FDA. If voluntary reporting of other drugs increased, the FDA's information would be more useful and timely.

Physicians must recognize that all the effects of new drugs have not been elucidated at the time of marketing. MedCenters Health Plan encourages physicians to report "serious" adverse drug events directly to the FDA, with FDA form 1639. If the task is deemed inconvenient, other health care professionals such as nurses or pharmacists can assist the physician in the reporting process. Documentation of all ADE should be made in the patient's medical record to prevent future problems. Please direct questions or requests for ADE reports form 1639 to Donna Schmidt (612) 927-2039. Direct questions to the FDA can be called to (301) 443-4580.

COMMUNITY ACQUIRED PNEUMONIAS (ADULT)

The majority of community-acquired pneumonias that occur in healthy ambulatory adults, are caused by a variety of pathogens such as mycoplasma, bacteria, viruses, chlamydia, rickettsial-like organisms and even parasites. Of these Mycoplasma pneumonia is considered the most common etiologic pathogen. Recent reports suggest that Legionella and Chlamydial species may account for a good portion of these pneumonias. However, most CAP hospital admissions consist primarily of patients older than 65 years. The average length of stay for these patients is 11.5 days and the fatality rate was 12.3 per 100 hospital discharges. Pneumonia is still ranked as the sixth leading cause of death in the United States with a mortality rate of 30-50%. Because seniors are more prone to influenza associated pneumonias they should be vaccinated each fall.

One reason management of CAP is so difficult is the variety of potentially causative pathogens. Streptococcus pneumonia accounted for 65% of the cases in the 1960's, but now reports show that it accounts for only 36%. The percent of pneumonia caused by L. pneumophilia, H. influenza,P. aeruginosa and others have substantially increased. This change of pathogens is reflected by a change in the usual effective drug therapy. After assessing the clinical situation or identifying the pathogen, choices of an oral antibiotic are listed in the table following.

AVERAGE WHOLESALE PRICE
OF 10-DAY SUPPLY OF ORAL ANTIBIOTICS

ME

	Suspected Pathogen	Possible Antibiotics			A
A.	Mycoplasma	Tetracycline	250mg	Q6H	2.70
	pneumonia	Doxycycline	100mg	Q12H	2.80
	Legionella	Eythromycin base	250mg	Q6H	3.20
	pneumonia	Erythromycin	333	Q8H	4.20
		EES	400	Q6H	6.00
B.	Strep pneumonia	Ampicillin	250mg	Q6H	2.00
		Amoxicillin	250mg	Q8H	2.70
		Penicillin VK	250mg	Q6H	6.00
	Grp A Strep	Cephalexin	250mg	Q6H	9.60
	Other Gram	Cephradine	250mg	Q6H	15.20
	postives	Cefadroxil	500mg	Q12H	38.45
		Cefuroxime	250mg	Q12H	38.45
	If penicillinase	Cloxacillin	250mg	Q6H	10.00
	producing	Dicloxacillin	250mg	Q6H	12.40
C.	Chlamydia (TWAR)	Tetracycline	250mg	Q6H	2.70
		Doxycycline	100mg	Q12H	2.80
D.	Hemophilus influenza	Amoxicillin	250mg	Q8H	2.70
	Branhamella	Tetracycline	250mg	Q6H	2.70
	catarrhalis	Doxycycline	100mg	Q12H	2.80
		TMP/SMX	DS	Q12H	3.20
	If beta-lactamase	AMOX/CLAV	250mg	Q8H	30.20
	producing				
E.	Pseudomonas	Ciprofloxacin	500mg	Q12H	36.00
	aeruginosa		750mg	Q12H	69.60
F.	Bacteroides fragilis	Metronidazole	250mg	Q6H	24.00
		Clindamycin	150mg	Q6H	36.82

Many concerns about concomitant medications which may increase risk of CAP in the elderly have been raised. Medications may act in an additive or synergistic manner with other age-related changes in immunity and underlying disease to enhance susceptibility to infections of the lung. Recently a study showed that hospitalized patients with NG tubes given cimetidine and antacids had a higher incidence of pneumonia than patients without H2 blockers .It remains extremely difficult to assess the relative impact of drug related derangements of lung defense systems.

JANSSEN BID

MedCenters is now receiving discounted prices on the following Janssen products: Imodium, Vermox, and Nizoral. However, please remember diphenoxylate/atropine is still the most economical antidiarrheal agent.

PARTNERS
National Health Plans

Drug Update

DRUG UPDATE
BUTTERWORTH HMO

MARCH 1989

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Newsletter Format

The Drug Update is a monthly newsletter written to Butterworth HMO Health Plan physicians and pharmacies to provide current information regarding rational and economical prescribing, formulary changes and drug therapy reviews. The newsletter is written in a summary format to minimize demands on the reader's time. Documentation and detailed information supporting conclusions is available upon request. Readers may wish to file the Drug Update in a three ring binder for future reference.

Formulary

A pocket sized copy of Butterworth HMO formulary will be mailed to all phyzicians and pharmacies. The formulary consists of four major parts: the introduction in the first 11 pages, a negative formulary, medication index, and maintenance medication list. The formulary is basically an open system, meaning that, drugs not listed either on the negative formulary or the medication index are still reimbursed by the Plan. The drugs listed are meant to be used as a guide in prescribing for this first year. Over the next year, the formulary will gradually change to a closed system where drugs not listed will not be reimbursed. Within each therapeutic class is a listing of drugs with a relative cost index preceding the name. The greater the number of "c's", the more expensive is the drug. In addition, drugs with the same number of "c's" are listed from least to most expensive. This cost index was included to facilitate economical choices of therapy.

Negative Formulary

Included within the formulary is a one-page list of drugs which are not covered by the Plan. When the physician prescribes a drug on this list and the pharmacist cannot dispense a covered equivalent, the pharmacist should contact the physician for an alternative. If no alternative exists, the pharmacist will inform the member that the prescription is not reimbursable by the Health Plan. In that case, the member is responsible for the entire cost of the presription. Items will be added and deleted from this list periodically with notification given to prescribers in the Drug Update.

Generic Substitution

Butterworth HMO maintains a list of drugs for which pharmacists are required to substitute generic equivalents if they receive a prescription written by brand name. A maximum allowable cost (MAC) has been assigned to each drug on this list (MAC list). The drugs included on the MAC list are marked with an asterisk (*) in the formulary.

Manufacturers of generic drugs must document that the product is bioequivalent to the brand name product in order to acquire marketing approval from the FDA. Although the FDA allows a statistical variability of +20% for evaluation of bioequivalency in human blood level studies, the average observed differences between generic and brand name products has been about + 3.5%. Most importantly, the FDA is not aware of a single documented case of bioinequivalence involving any generic drug product that has been approved by the FDA as bioequivalent. In addition, the Bioequalence Task Force of the FDA has just recently concluded that there was a remarkable lack of hard evidence substantiating claims of bioequivalency problems with generic drugs. Therefore, Butterworth HMO Health Plan is comfortable with requiring generic substitution for those products included on our maximum allowable cost (MAC) list.

Some drugs for which generic equivalents are available have been intentionally excluded from the MAC list. These products include Lanoxin, Dilantin, Tegretol, Procan SR, sustained release theophyllines, Synthroid, Premarin and Provera. If a physician wants the brand name product to be dispensed for a drug marked with an asterisk in the formulary, (s)he must write dispense as written (DAW) on the prescription. Otherwise a generic product will be dispensed. For every DAW prescription, the physician must write a patient specific letter to the Health Plan regarding the medical reason(s) the brand name product is needed.

Maintenance Medication

The Health Plan's policy states that members may not receive more than a 30 day supply of any medication. Exceptions to this policy are drugs specifically listed on the maintenance medication list. Items on this list may be dispensed in maximum quantities of a 30 day supply or 100 units, whichever is greater, but should not exceed a 100 day supply. This list is intentionally restrictive.

Drug Use Review

A formalized drug use review program authorized by PARTNERS Pharmacy and Therapeutics Committee will be implemented this month. The goal of this system is to assure the quality and efficiency of drug use by increasing physician awareness of efficacy, safety and cost issues. This program's goal is to minimize needless expenditure of resources by eliminating care which does not increase quality or improve outcome and recommendations regarding these issues can be made to the Pharmacy and Therapeutics Committee.

Efforts will focus on the top fifty prescription drugs to determine those target drugs which have less expensive, equally safe and effecacious alternatives. Physicians who are frequent prescribers of expensive medications, such as terfenadine (Seldane) and cefaclor (Ceclor), can expect letters from PARTNERS which identify alternative drugs which may be appropriate in many instances. PARTNERS will also provide physicians with other reports, such as their non-formulary and controlled substances prescribing habits. Physicians can use this information as a tool to identify formulary alternatives, evaluate their own prescribing patterns and monitor incidence of undesirable outcomes.

PARTNERS
National Health Plans

Drug Update

JUNE 1989

Editors: Donna Schmidt, [illegible]
Allan A. Abramson, M.D.

MedCenters Pharmacy and Therapeutics Committee has made many formulary decisions. Many drugs were not added to the formulary because they did not offer any therapeutic advantage over the current formulary drugs. The following chart is a summary of the formulary decisions:

KEY: F = formulary R = restricted NF = nonformulary NC = not covered
RA = prior authorization requested

NEW DRUGS

terconazole (Terazol)	F
mupirocin ((Bactroban)	R
pirbuterol (Maxair)	F
diclofenac (Voltaren)	F
ursodiol (Actigal)	R
dexamethasone/tobramycin (Tobradex)	F
prednisolone/gentamicin (Pred G)	F
misoprostol (Cytotec)	RA
diltiazem SR (Cardiazem SR)	F
cholestyramine bar (Cholybar)	NC
flurbiprofen (Ansaid)	NC
tiopronin (Thiola)	F
flutamide (Eulexin)	F
octreotide (Sandostatin)	F
oxacillin (Prostaphlin)	NC
glycopyrolate oral, inhaled	F
atropine, inhaled	F
triethanolamine/chlorobutanol (Cerumenex)	NC
astemizole (Hismanal)	NC
nicardipine (Cardene)	NC
oxiconazole (Oxistat)	NC
carteolol (Cartrol)	NC
enoxacin (Comprecin)	NC
mefenamic acid (Ponstel)	NC
famotidine (Pepcid)	NF

DILTIAZEM SR Diltiazem (Cardiazem SR) is indicated for the treatment of hypertension alone or with other antihypertensives. It was added to the formulary due to the relative advantages of diltiazem's least negative inotropic effects and low incidence of constipation when compared to verapamil. Its usage is limited to patients for whom those side effects might prove troublesome. Dosing recommendation: 90 mg to 180 mg BID.

DICLOFENAC Diclofenac (Voltaren) is a nonsteroidal anti-inflammatory drug used for treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The Committee recommends prescribing other drugs before diclofenac, but since it does have a possible role for some patients, it has been added to the formulary. The starting dose for osteoarthritis is 50 mg BID which would cost $40.80 for a month's supply.

ASTEMIZOLE Astemizole (Hismanal) is a long-acting antihistamine. Since the drug would need to be discontinued for 45 days before allergy visits or attempts at pregnancy due to its long half life, it was not added to the formulary. Terfenadine (Seldane) is recommended as an alternative.

FLURBIPROFEN Flurbiprofen (ANSAID) is a nonsteroidal antiinflammatory agent in the proprionic acid class (as are ibuprofen & naproxen). It offers no major therapeutic gain in the treatment of rheumatoid arthritis or osteoarthritis, so it was not added to the formulary.

DESIPRAMINE Desipramine has been removed from our current Maximum Allowable Cost (MAC) list. This allows the physician to write for a brand name desipramine (i.e. Norpramin) and the pharmacist will receive the appropriate payment. A generic substitution can still occur unless the prescription for the brand name contains a DAW (Dispense As Written).

H2 BLOCKERS All drugs in this category are still considered equally effective. Therefore, cimetidine (Tagamet) was again chosen as the preferred H2 blocker since occurrence of adverse effects is rare. Cost then becomes the key factor in prescribing decisions. At all dose comparisons, Tagamet provides a substantial cost advantage over Zantac. Zantac is less expensive than Pepcid. Since the manufacturers of Pepcid do not participate in volume discounts and it is more expensive, Pepcid was changed to nonformulary status.

FOOTNOTE Quinidex, Entolase and Entolase HP are all on the medication formulary. The NF (nonformulary) legend does not apply to these drugs.

MISOPROSTOL Misoprostol (Cytotec) has been added to the Restricted category of the formulary. Cytotec has been approved for prevention of NSAID-induced gastric ulcers in patients with a high risk of complications from a gastric ulcer. It has no effect compared to placebo on gastrointestinal pain or discomfort associated with nonsteroidal use. It has not been proven to prevent GI bleed associated with nonsteriodals. Most studies of misoprostol have been in patients with duodenal or gastric ulcers unrelated to nonsteriodals. It has been about as effective as cimetidine or ranitidine in promoting the healing of duodenal or gastric ulcers, but less effective in relieving pain. Misoprostol also has a much higher incidence of adverse reactions; diarrhea, abdominal pain, headache, bleeding in early pregnancy, with partial or complete expulsion of uterine contents. Recommended dosage is 200 mcg QID with meals for the duration of the NSAID therapy. Cost for one month's supply at this dose is $59.70. There is some evidence that 200 mcg BID (half dose) could be just as effective.

CONTRAINDICATIONS AND WARNINGS:
Women of child bearing age who require NSAID therapy and are at high risk of complication should receive misoprostol only if she:

- is capable of complying with effective contraceptive measures;
- has received both oral and written warnings of the hazards of misoprostol, the risk of possible contraception failure, and the danger to other women of childbearing potential should the drug be taken by mistake;
- has a negative serum pregnacy test within two weeks prior to beginning therapy; and
- will begin Cytotec only on the second or third day of the next normal menstrual period.

CRITERIA OF USE:
Approved for prior authorization and the following revised criteria:

- patient must be on NSAID, AND
- have diagnosed gastric disease/GI bleed, OR
- dyspepsia temporally related to a NSAID.

The physician may use his/her medical expertise to decide when to prescribe misoprostol for the elderly but prior authorization is still required.

NEW DRUG THERAPY A short analysis of MedCenters average cost of new drugs within a therapeutic class, increased 33% from 1986 to 1987 and 49% from 1987 to 1988.

Drug Update

MEDCENTERS HEALTH PLAN

OCTOBER 1989 Editors: Robert Straka, Pharm.D. Leonard Nordstrom, M.D.
Donald Duncan, M.D. Donna Schmidt, Pharm.D.

INTRODUCTION Beta-adrenergic blocking agents are among the most widely prescribed therapeutic agents available today. Owing to the number of available agents and variability of drug properties, beta-blockers demonstrate utility in a variety of disease states. The following introduction to the basic properties of this drug class is designed to facilitate better clinical utility of these agents for a given patient.

CARDIO SELECTIVITY Cardioselective beta-blockers are those agents which preferentially block beta-1 receptors at lower doses. Although atenolol, metoprolol, and acebutolol are cardioselective, they are not cardiospecific. They have a lower potential to increase airway resistance but are not free of this side effect. Beta-blockers, even those with apparent cardioselectivity, should not be used in patients with asthma or a history of obstructive airway disease unless no alternative treatment is available. Patients who have a tendency towards obstructive airway disease or asthma must be treated with great caution and may require increased doses of their beta-2 agonists to overcome the blockade of the bronchial adrenoceptors.

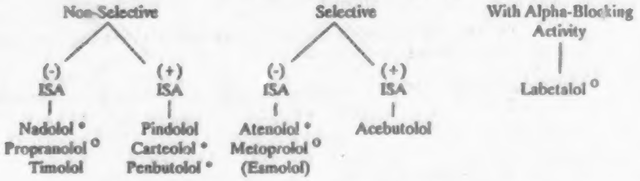
HYPOGLYCEMIA Beta-blockers may diminish glucose tolerance in diabetics. They also interfere with metabolic and autonomic responses to hypoglycemia. Though beta-blockers are not contraindicated for diabetics, their use is best avoided in those who experience frequent episodes of hypoglycemia. Other diabetics requiring beta-blocker therapy generally experience fewer side-effects with the cardioselective agents.

ISA Intrinsic sympathomometic activity (ISA) represents the capacity of beta-blockers to stimulate as well as to block adrenergic receptors. Drugs demonstrating ISA (+) are useful in patients intolerant of further reductions in heart rate or patients who already have low HDL or high triglyceride levels. Pindolol and carteolol exhibit greater ISA than penbutolol and acebutolol.

ALPHA BLOCKADE Labetalol with its alpha blocking properties tends to lower blood pressure without a reflex tachycardia or significant reduction in heart rate. In fact, it may have the potential to lower peripheral resistance. In spite of these effects, labetalol lacks any major advantages over the other beta blockers.

The following figure illustrates the various properties of beta blockers.

Beta-Adrenoceptor Blocking Drugs



* . Primary renal excretion, more water soluble, less sleep disturbance, change dosage interval in renal failure

o Primarily hepatic metabolism, more lipid soluble (and more CNS side effects)

HYPERTENSION

Beta-blockers are effective antihypertensive drugs but their mode of action is not completely understood. However, the collective characteristics of beta-blockers in reducing cardiac output, altering baroreceptor reflex sensitivity and blocking peripheral adrenoceptors are unquestionably related to their antihypertensive effectiveness. Some beta-blockers depress plasma renin secretio Despite the many contraindications, blood pressure can usually be controlled with relatively fe. side effects. In general the dose of beta-blocker does not have to be as high as originally thought. The maximum dose of propranolol is probably 320mg daily. Atenolol can usually be given in a dose of 50mg daily and it is rarely necessary to increase to 100mg.

ANGINA

Beta-blockers improve exercise tolerance and relieve symptoms in patients with angina, this effect caused by their reduction of cardiac work. No single drug is superior to another in this class, though occasionally a patient will respond better to one beta-blocker than to another. There is some evidence that sudden withdrawal may cause exacerbation of angina, therefore gradual reduction of dose is preferable when beta-blockers are to be stopped. There is a risk of precipitating heart failure when beta-blockers and verapamil or diltiazem are used together in patients with established ischemic heart disease.

COST

As demonstrated in the table below, there is considerable cost variance amongst beta-blockers, since only Inderal is generically available

Table 1. Average Wholesale Price for 30 day supply of beta blockers at low maintenance doses

propranolol (generic)	40mg BID	2.40
penbutolol (LEVATOL)	20mg QD	17.20
propranolol long acting (INDERAL LA)	80mg QD	18.25
atenolol (TENORMIN)	50mg QD	18.95
nadolol (CORGARD)	40mg QD	19.14
* propranolol (INDERAL)	40mg BID	20.47
metoprolol (LOPRESSOR)	50mg BID	21.90
acebutolol (SECTRAL)	400mg QD	22.16
timolol (BLOCADREN)	10mg BID	23.75
labetalol (NORMODYNE)	200mg BID	23.98
pindolol (VISKEN)	5mg BID	29.70
carteolol (CARTROL)	10mg QD	35.63

* for information only; the brand name Inderal is not covered.

SELECTION

Some of the beta-blockers we have been discussing are not covered by the plan. The two beta-blockers which are most useful are propranolol and atenolol. These drugs should be considered first when choosing a beta blocker. (Group A)

In order to illustrate properties of the entire beta blocker class, we have discussed some drugs which are not reimbursed by the Plan. Table 2 shows the formulary status of each beta blocker.

Table 2: Formulary Status

formulary to be (group A): used first	formulary to be (group B): used second	negative formulary
propranolol (generic Inderal) propranolol LA (INDERAL LA) atenolol (TENORMIN)	acebutolol (SECTRAL) pindolol (VISKEN) labetalol (NORMODYNE) metoprolol (LOPRESSOR) nadolol (CORGARD)	timolol (BLOCADREN) carteolol (CARTROL) penbutolol (LEVATOL)

FORMULARY ADDITIONS

New beta-blockers like betaxolol (Kerlone), dilevalol (Unicard) and celiprolol (Selectrol) will not be reimbursed until a decision is made by Pharmacy and Therapeutics Committee.

PARTNERS
National Health Plans

Drug Update

Update on Nonsteroidal Anti Inflammatory Drugs By: John T. Schousboe M.D.
A condensed version from the Bulletin Vol 32 No.1 1988

November 1989

Editors: Cynthia Anderson, Pharm.D. (612) 897-2939
Edward J. Smith, M.D.

Use Of Nonsteroidal Anti-Inflammatory Drugs

A review of the therapeutic use, toxicology and cost of good NSAIDs is timely for many reasons. First, despite their widespread use, the mechanisms of action of NSAIDs and their relation to the therapeutic and toxic effects of these drugs remains incompletely understood. Second, there is now a bewildering number of these agents on the market, but no clear guidelines regarding their selection in specified clinical situations. Third, some data has emerged in the last decade defining the side effects of these drugs, and some potential differences among them. Most authors over the past 15 years have ascribed the therapeutic efficacy of NSAIDs to their ability to inhibit cyclo oxygenase and thereby prostaglandin synthesis. Certain prostaglandins play a significant role in the development of inflammation and pain by increasing vascular permeability and stimulation of pain nerve endings by kinin. However, there is some evidence that prostaglandin synthesis inhibition may not be the only mechanism.

Therapeutic Uses

In both rheumatoid arthritis and osteoarthritis, no single subgroup of NSAIDs have been shown consistently more effective than others, but for individual patients certain NSAIDs may be more effective. For ankylosing spondylitis, indomethacin and naproxen were more effective than fenoprofen, ibuprofen, tolmetin, with aspirin as the least effective. Large dosages (150-200 mg QD indomethacin or 1500 mg QD naproxen) are needed initially and then after two to three days the dosage is lowered and then tapered off over 5 to 10 days. In acute gout salicylates are clearly less effective and should not be used.

Cost

While there may be a few differences among the NSAIDs in efficacy in arthritis illnesses, and only slight differences in toxicity profiles, there are considerable differences in the cost of these agents. Most of the NSAIDs cost two or more times as much as aspirin products and generic ibuprofen and indomethacin. As a therapeutic class, NSAIDs are consistently in the top three classes by cost and volume at PARTNERS Health Plan of the MidAtlantic. Our choice of NSAIDs for our patients should be carefully considered, because many patients remain on NSAIDs for years, generating high drug costs.

TABLE 1 Average Wholesale Price for 30 day supply of NSAIDs

	Dosage	AWP
Enteric coated ASA	1.95 gm BID	10.80
Ibuprofen	800 mg TID	*9.90
Indomethacin	50 mg TID	*8.10
Salsalate	1.5 gm BID	39.92
Naproxen	500 mg BID	52.76
Fenoprofen	600 mg TID	52.30
Ketoprofen	75 mg TID	59.00
Sulindac	200 mg BID	58.05
Tolmetin	400 mg TID	55.72
Piroxicam	20 mg QD	49.88
Diclofenac	75 mg TID	70.90
Mecofenamate	100 mg TID	54.45

* Average generic prices.

Selection

Because NSAIDs have a somewhat unpredictable efficacy in any one individual, a trial of a few or even several is sometimes necessary before finding one that reasonably reduces the patient's pain and inflammation. These agents generally will exhibit their full therapeutic effect within one to two weeks and a trial one of these medicines for chronic pain or arthritis need not exceed this time period.

Table 2 shows PARTNERS Health Plan of the MidAtlantic preferred sequence of NSAIDs to be tried for most patients with chronic inflammatory arthritis. This list emphasizes the least expensive agents first, which is reasonable in the absence of compelling differences between them in terms of efficacy, convenience or toxicity.

TABLE 2 Order of NSAIDs to be tried in appropriate patients with chronic inflammatory arthritis

1. Enteric-coated aspirin
2. Ibuprofen
3. Indomethacin
4. Naproxen
5. Piroxicam

Acute Musculo-Skeletal Pain

For acute musculo-skeletal pain the drug of choice is ibuprofen. Other NSAIDs have not been demonstrated to have clinical superiority.

Particular NSAIDs may be preferred if the patient has other conditions or problems that predispose them to particular side effects as shown in Table 3.

TABLE 3 Preferred NSAIDs in Certain Circumstances

	Condition	Preferred Choices
1.	Peptic ulcer	Nonacetylated salicyclates
2.	Renal insufficiency	Sulindac,Nonaceylated salicyclates
3.	Hypertension (difficult to control)	Nonacetylated salicyclates
4.	Chronic anticoagulation	Nonacetylated salincyclates
5.	ASA hypersensitivity	Nonacetylated salincyclates
6.	Hearing loss,tinnitus	Avoid salicylates
7.	Poor compliance with multiple daily dosing	piroxicam,naproxen, sulindac, diflunsal

GI Toxicity

What NSAID is preferable to use in patients with a history of peptic ulceration or symptomatic gastric irritation? It appears clear that enteric-coated aspirin is preferrable to plain or buffered aspirin. Some authors have asserted that NSAIDs with short half-lives may be less ulcerogenic in the elderly, but there is no firm data to confirm this hypothesis. Perhaps the safest of these drugs, especially in the presence of active peptic ulcer, are the nonacetylated salicylates such as salsalate and choline magnesium trisalicylate. Another strategy for patients who have had gastric side effects with NSAIDs is to administer them along with an H2 antagonist. Unfortunately, to date there has not been much documentation that this is particularly efficacious. PARTNERS Health Plan of the MidAtlantic recommends that H2 blockers not be routinely prescribed for prevention of NSAID gastropathy, except in selected patients.

PARTNERS
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Drug Update

TREATMENT OF RESPIRATORY TRACT INFECTIONS IN ADULTS: SPOTLIGHT ON CECLOR

Editors: Cynthia A. Anderson, Pharm.D. (612) 897-2939
John Shevlin, R.Ph.
Paul Berger, M.D.

CECLOR is a broad spectrum antibiotic finding particular utility in pediatric otitis media therapies where rotation of drugs is required to adequately treat the chronically reinfected child and avoid resistant organism development. CECLOR's place in treating adult respiratory infections is less well-established, however. In fact, CECLOR fails to appear as drug of choice in the Guide to Antimicrobial Therapy, 1989 by Jay P. Sanford, M.D. for treatment of infections at any body site. Despite this, prescribing of CECLOR capsules significantly outnumbered prescriptions for CECLOR suspension at PARTNERS Health Plan of Georgia in second quarter, 1989. What follows is a brief review of the common etiologies, treatments and therapy costs of adult respiratory infections.

BRONCHITIS Acute bronchitis in adolescents and adults free of underlying host defects is most commonly caused by Mycoplasma. Erythromycin is the agent of choice for treating this microbe. Occasionally, H. influenza is the causative organism and is successfully treated with amoxicillin or ampicillin.

Chronic bronchitis patients usually demonstrate the dual problem of inadequate host defenses and less predictable causative organisms. However, the vast majority of insulting microbes are S. pneumonia, H. influenza or B. catarrhalis. Amoxicillin and ampicillin will successfully treat most of these infections, with tetracycline and TMP/Sulfamethoxazole (Bactrim, Septra) listed as alternative therapies. Augmentin (amoxicillin/clavulanate) may occasionally be called upon for treatment of beta-lactamase positive H. influenza or B. catarrhalis.

PROPHYLAXIS The advisability of prophylactic treatment for chronic bronchitis is still debatable. If prophylaxis is deemed appropriate, rotation of agents is required to discourage development of resistant organisms.

PNEUMONIA Community-acquired bronchopneumonia in otherwise-healthy adults is commonly associated with S. pneumonia, Mycoplasma, Legionella or Chlamydia. Erythromycin is the drug of choice for treating these microbes, with tetracycline listed as an alternative. Community-acquired pneumonias in patients having chronic bronchitis should be treated according to the chronic bronchitis regimen listed above.

CECLOR CECLOR, while comparable to Augmentin in its ability to eradicate infections due to B. catarrhalis and beta-lactamase positive H. influenza, is not recommended as either drug of choice or alternative choice in treating adult respiratory infections. As Table 1 demonstrates, the cost of 10-day CECLOR therapy is significantly higher than those associated with other therapies mentioned above and detailed in Table 2.

Table 1: Average Wholesale Price of 10-day CECLOR Therapy

CECLOR 250 mg capsule	TID	$41.80
CECLOR 500 mg capsule	TID	$82.13

Table 2: Average Wholesale Price of 10-day Therapy to Treat Adult Respiratory Infections

Disease	State	Drug of Choice	Alternative Drug	Schedule	Cost
Bronchitis,	Acute	Erythromycin E.S. 400mg		QID	6.40
			Ampicillin 250mg	QID	2.40
			Ampicillin 500mg	QID	3.80
			Amoxicillin 250mg	TID	2.70
			Amoxicillin 500mg	TID	5.25
Bronchitis,	Chronic	Ampicillin 250mg		QID	2.40
		Ampicillin 500mg		QID	3.80
		Amoxicillin 250mg		TID	2.70
		Amoxicillin 500mg		TID	5.25
			Augmentin 250mg	TID	35.20
			Augmentin 500mg	TID	56.82
			Tetracycline 250mg	QID	1.20
			Tetracycline 500mg	QID	1.80
			TMP/Sulfa DS	BID	2.40
Pneumonia, (No underlying illness)	Community-acquired	Erythromycin E.S. 400mg		QID	6.40

SUMMARY

Cephalosporins are an obvious choice as safe and effective alternatives to the penicillins for penicillin-allergic individuals. As demonstrated in this article, other effective alternatives exist. Erythromycin, TMP/Sulfa DS and Tetracycline are all effective against H. influenza, S. pneumonia and B. catarrhalis, though tetracycline is less predictably so. CECLOR, an effective agent against B. catarrhalis and beta-lactamase positive H. influenza, is neither recommended as first or second choice therapy nor recommendable as cost-effective in treating respiratory infections caused by these microbes.

PARTNERS HEALTH PLAN OF GEORGIA POLICY

PARTNERS HMO of Georgia requests that CECLOR use be restricted to pediatric populations owing to the wealth of other effective agents for adult infections and because of the high cost of CECLOR.

PARTNERS AUGMENTIN POLICY

PARTNERS suggests that Augmentin use be reserved for chronic bronchitis patients for whom strong evidence of B. catarrhalis or beta-lactamase positive H. influenza exists and for whom treatment with other agents has failed.

PHARMACY AND THERAPEUTICS COMMITTEE

Drug Review

I. **DRUG:** Fluconazole (Diflucan, Pfizer) FDA Classification IAA

II. **AHFS CATEGORY:** 8:12.04 Oral Antifungal Agent

III. **SIMILAR FORMULARY AGENTS:** Clotrimazole, Ketoconazole

IV. **DESCRIPTION:** Fluconazole is an antifungal agent. Fluconazole differs from some of the other antifungal agents in that it is a triazole containing three nitrogens in its azole ring.

V. **PHARMACOLOGY:** Triazole agents are pharmacologically similar to imidazole agents. The primary mechanism of action is inhibition of ergosterol biosynthesis resulting in an accumulation of precursor intermediates to ergosterol. The compound may also cause direct damage to membrane phospholipids. Further, fluconazole may inhibit cytochrome C oxidative and perioxidative enzymes resulting in increases in intracellular peroxide generation.

Fluconazole has been observed to be efficacious in vivo animal models of aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, and histoplasmosis.

VI. **PHARMACOKINETICS:** Fluconazole is well absorbed after oral administration reaching peak plasma concentrations 2-6 hours after dosing. It has a volume of distribution of 0.8 L/kg and is only 11% protein bound. The bioavailability of fluconazole following oral administration has been measured to be over 90%.

Fluconazole penetrates the CNS. The concentration ratios of plasma to CNS are 73.8% at 50mg/day and 88.7% at 10mg/day regardless of meningial inflammation (1,4). There appears to be a prolonged half-life in the cerebrospinal fluid. Serum half-life is 22 hours, allowing once daily administration. Fluconazole is primarily renally eliminated with over 90% of the administered dose unchanged in the urine. The elimination half-life is prolonged in patients with renal deficiency.

VII. **INDICATIONS:** Fluconazole is approved by the FDA for treatment of oropharyngeal and esophageal candidiasis and cryptococcal meningitis. Fluconazole is also indicated for the treatment of serious systemic candida infections including urinary tract infections, peritonitis and pneumonia.

VIII. **LITERATURE REVIEW:**

Am J Med 1988; 85:477-481
Lancet 1989; (1):746-748
J Infect Dis 1988; 158(4):903-904
Antimicrob Agents Chemother 1988; 32(3):369-373

IX. **ADVERSE EFFECTS:** In clinical trials, fluconazole has been well tolerated. The most common adverse reactions reported are nausea, abdominal pain, and headache. Reversible elevation in LFTs has been reported.

X. **DRUG INTERACTIONS:** Fluconazole may increase cyclosporin, phenytoin, hypoglycemic, and warfarin concentrations; and may decrease ethinyl estradiol AUC. Rifampin and cimetidine may decrease fluconazole serum concentrations.

XI. **CLINICAL STUDIES:** Controlled double-blind study compared fluconazole and ketoconazole in treatment of orapharyneal candidiosis in patients with AIDS. Cultures were negative in 87% of the fluconazole group and 69% of the ketoconazole group. A blinded open-label, multicenter study compared fluconazole and clotrimazole and reported 96% cure rate for fluconazole, and 89% cure rate for clotrimazole.

XII. **DOSING INFORMATION:** For systemic candidiasis, the recommended dose is 400mg load followed by 200mg/day for a minimum of 4 weeks.

For cryptococcal meningitis, 400mg load followed by 200mg to 400mg/day for 10 to 12 weeks after the CSF becomes culture negative.

Dose should be reduced in patients with renal deficiency. For prophylaxis against fungal meningitis and relapse, 100-400mg/day.

XIII. **COST COMPARISON (Based on AWP):**

Drug	Dosage	Cost/Dose	Cost/Day
Clotrimazole	10mg/troche	0.56	2.80
Ketoconazole	200mg	1.03	1.03-4.12
Fluconazole	100mg	6.88	13.75-27.52

(Amphotercin B 50mg/vial, 20.00/intrathecal dose)

XIV. **RECOMMENDATION:**

1. Add Fluconazole to the formulary for treatment of cryptococcal meningitis.

2. Add fluconazole to formulary. RESERVED when used for the treatment of oropharyngeal, esophageal, or systemic candidiasis. Adequate trials of clotrimazole and/or ketoconazole must be attempted prior to fluconazole where appropriate (eg. clotrimazole for oropharyngeal candidiasis).

XV. **ACTION:** Add fluconazole to the formulary when used for

1. Histoplasmosis, Cryptococcal or Cocciodial meningitis OR

2. Oropharyngeal or esephageal candidiasis after adequate trials of Mycelex troches and Ketoconazole OR

3. Systemic candidiasis after an adequate trial of ketoconazole.

PHARMACY AND THERAPEUTICS COMMITTEE

Drug Review

I. **DRUG:** Nafarelin (Synarel, Syntex)

II. **AHFS CATEGORY:** 68:18 Gonadotropins

III. **SIMILAR FORMULARY AGENTS:** None, though danazol, medroxyprogesterone and oral contraceptives are therapeutically similar.

IV. **DESCRIPTION:** An analog of gonadotropin releasing hormone (GnRH) which effects decreased pituitary secretion of gonadal steroids.

V. **PHARMACOKINETICS:** Rapidly absorbed into systemic circulation following intranasal administration with peak serum concentrations occuring within 30 minutes, and serum half-life of about 3 hours. Induces amenorrhea rates of 65%, 80% and 90% in patients after 60, 90 and 120 days, respectively. Normal menstrual cycles returned in 80% and 100% of patients by second and third post-treatment months, respectively.

VI. **APPROVED INDICATIONS:** For management of endometriosis, including pain relief and reduction of endometriotic lesions.

VII. **LITERATURE REVIEW:**

NEJM 1988; 318:485-489
Fertil Steril 1985; 44:583-588
Clin Pharmacol Ther 1988; 44:275-282

VIII. **ADVERSE REACTIONS:** (During 6 month treatment)

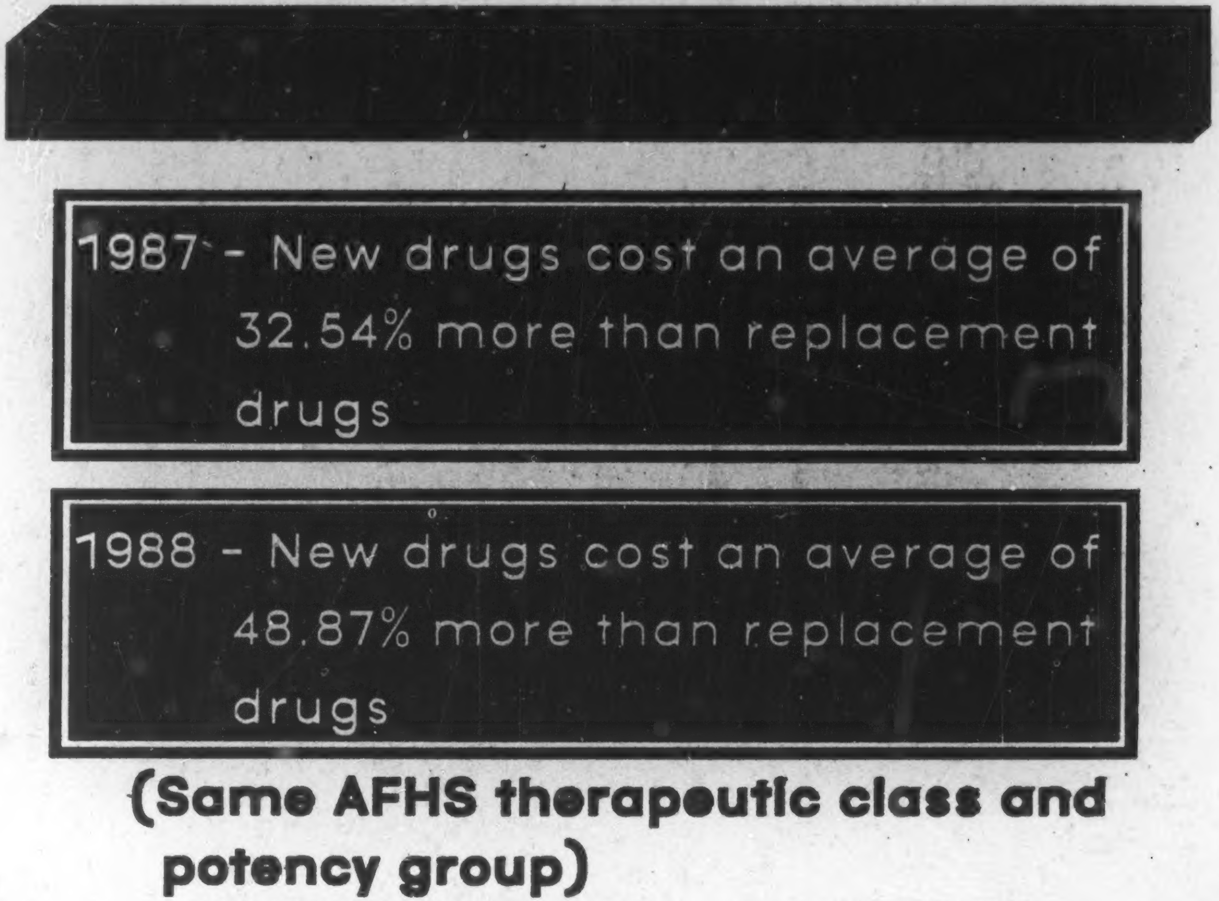
	Treatment Received	
	Nafarelin %	Danazol %
Hot Flashes	90	69
Decreased Libido	22	7
Vaginal Dryness	19	6
Headaches	19	21
Emotional lability	15	18
Insomnia	8	4
Acne	13	20
Myalgia	10	23
Breast Size Reduction	10	16
Edema	8	22
Seborrhea	8	18
Weight Gain	3	6
Increased Libido	2	6
Nasal Irritation	10	3
Depression	2	5
Hirsutism	2	6

IX **DOSING INFORMATION:** One 200mg spray BID, alternating nostrils. Therapy to commence between days 2 and 4 of the menstrual cycle. If amenorrhea is not accomplished by the end of two months of treatment, increase dose to 400mg (two sprays) into one nostril BID, again alternating nostrils between morning and evening administrations. Dosing regimen is to continue for 6 months.

X. **COST COMPARISON:**

Drug	Dose	AWP Cost 30 day supply
Danazol	200mg BID	$114
Danazol	400mg BID	$228
Nafarelin	200mg BID	$282

XI. **RECOMMENDATION:** Add to the formulary with prescribing limited to OB/GYN specialty practitioners.



1987 - New drugs cost an average of 32.54% more than replacement drugs

1988 - New drugs cost an average of 48.87% more than replacement drugs

(Same AFHS therapeutic class and potency group)

Utilization of an Analytical Rating Tool (A.R.T.) to Assist in H_2 Antagonist Formulary Selection

Cynthia A. Anderson*, Corinne Schroeder
PARTNERS National Health Plans
Minneapolis, Minnesota

OBJECTIVES

- Utilize A.R.T. for Evaluation of H_2 Antagonists
- Determine H_2 Antagonist(s) of Most Value to PARTNERS

THE A.R.T. PROGRAM

- Computerized tool designed to assist in drug analyses and the formulary selection process.
- Allows integration of clinical assessment, cost analysis, and compliance considerations inherent to quality formulary selection process.
- Provides consistent, systematic format for evaluation of multiple therapeutic categories.

WHY H_2 ANTAGONISTS?

- Account for 7.4% of the drug budget
- Consistently one of the top five prescribed therapeutic classes
- Wide therapeutic index, therefore potential to significantly impact pharmacy budget.

RESULTS

- Cimetidine determined to be the H_2 Antagonist of most value to PARTNERS.
- Ranitidine should be used if patient is currently on interacting drugs or at high risk for adverse effects.

ESTABLISH TEMPLATE FOR H_2 ANTAGONIST COMPARISON

A. Select Agents for Comparison

- cimetidine
- famotidine
- nizatadine
- ranitidine

B. Analyze Information

- Perform comprehensive medical literature search for H_2 Antagonist.
- Include studies regarding; efficacy, adverse effects, pharmacokinetics, outcomes, individual agents and comparative studies.
- Scrutinize the search.
  - Select 30 - 40 key articles to support H_2 Antagonist evaluation
- Create a bibliography

C. Identify Key Criteria

- Identify comparative criteria for the evaluation of the H_2 Antagonists.
  - Labeled Indications
  - Potential adverse effects
  - Potential drug interactions
  - Pharmacokinetics
  - Ease of use
  - Cost

D. Create Profiles

- Create a table of comparison for each of the six key criteria.
- Detail each drug's characteristics within each of the criteria profiles.

PERFORM COMPARISON OF H_2 ANTAGONISTS

A. **Enter Data**

- Enter H_2 Antagonists, key criteria, and comparative profiles into A.R.T. program software.

B. **Weigh Key Criteria**

- Assign a relative weight to each of the key criteria identified for H_2 Antagonist comparison.
- Base weight upon subjective importance placed upon these criteria in the formulary selection process.
- Weigh on scale from 1 to 99

1 = least important
99 = most important

C. **Rank H_2 Antagonists**

- View comparative profiles
- Assign a relative rank of favorability to each H_2 Antagonist within the comparative profiles.
- Rank on scale from 1 to 99

1 = least favorable profile
99 = most favorable profile

D. **Determine H_2 Antagonist of Most Value**

- Upon completion of weight and rank process, A.R.T. tabulates cumulative drug scores.

Drug Score = The Sum of the Relative Weights of Comparative Criteria Multiplied by Rank of the Drug within the Comparative Profile

- Score reflects drug value

Highest score = most value

FUTURE APPLICATIONS

- Oral Hypoglycemic Agents
- Nonsteroidal Antinflammatory Agents
- Beta Blockers
- Diuretics
- ACE Inhibitors
- Antihistamines
- Antidepressants

- ART ^{R} and Beta Blockers

Donna Schmidt, Pharm.D.
Manager, Clinical Pharmacy Program
PARTNERS National Health Plan

I. Introduction

II. Drug Comparison Scores

The drugs in this classification have been scored based on the profile weight factors and drug weight factors within each profile. The higher the score for a particular drug the more favorable the drug is to use.

Drug	Score	Drug	Score
Acebutolol	15.0	Pindolol	8.4
Atenolol	15.0	Propranolol	6.5
Carteolol	8.4	Propranolol LA	7.0
Labetolol	5.4	Timolol	5.1
Metoprolol	13.9		
Nadolol	7.6		
Penbutolol	7.3		

III. Profile Weight

Profile	Weight factor		
Cost	25	....	6.4%
Pharmacokinetics	75	....	19.2%
Pharmacology	90	....	23.1%
Potential Adverse Drug Reaction	75	....	19.2%
Indications	75	....	19.2%
Drug Interactions	50	....	12.8%

- Percentages based on sum of assigned weight factors.

IV. Profile Descriptions

A. Cost

Cost 6.4%	Weight factor	Low Maintnn adult dose	Cost/Month AWP*	Cost/Month Actual	
Acebutolol	25	400 mg bid	22.16		
Atenolol	75	50 mg qd	18.95		
Carteolol	15	15 mg qd	53.43		
Labetolol	90	200 mg bid	22.74		
Metoprolol	50	50 mg bid	21.90		
Nadolol	75	40 mg qd	19.14		
Penbutolol	85	20 mg qd	16.50		
Pindolol	25	5 mg bid	25.70		
Propranolol	90	40 mg bid	2.40		
Propranolol LA ...	80	80 mg qd	18.25		
Timolol	50	10 mg bid	24.74		

B. Pharmacokinetics

Pharmacokinetics 19.2%	Weight factor	t1/2 (hours)	Active Metabolites	Route of Elimination	
Acebutolol	35	3 - 4	Yes	H/R	
Atenolol	80	6 - 9	No	R	
Carteolol	65	5 - 6	ISD	R/H	
Labetolol	70	5 - 8	No	H	
Metoprolol	80	3 - 4	No	H	
Nadolol	90	14 - 24	No	R	
Penbutolol	50	5 - 6	ISD	H	
Pindolol	75	3 - 4	No	R/H	
Propranolol	10	3 - 5	Yes	H	
Propranolol LA ...	30	8 - 11	Yes	H	
Timolol	15	2 - 5	ISD	H	

C. Pharmacology

Pharmacology 23.1%	Weight factor	Beta-1 Selective	Alpha Blockade	ISA	Lipid Solubility
Acebutolol	85	++	0	+	Low
Atenolol	50	++	0	0	Low
Carteolol	35	0	0	++	Low
Labetalol	25	0	+	0	Moderate
Metoprolol	50	++	0	0	Moderate
Nadolol	25	0	0	0	Low
Penbutolol	15	0	0	+	High
Pindolol	25	0	0	+++	Low
Propranolol	10	0	0	0	High
Propranolol LA ...	10	0	0	0	High
Timolol	10	0	0	0	Moderate

D. Potential Adverse Drug Reaction

Potential Adverse Drug Reaction 19.2%	Weight factor	Bronchospasm	Cardiac Failure*	Response to Hypoglycemia	Withdrawal Reaction
Acebutolol	85	0/+	0/+	normal	0/+
Atenolol	75	0/+	+	normal	+
Carteolol	25	+	0/+	impaired	0/+
Labetalol	0	+	+	impaired	+
Metoprolol	50	0/+	+	normal	+
Nadolol	0	+	+	impaired	+
Penbutolol	50	+	0/+	impaired	0/+
Pindolol	50	+	0/+	impaired	0/+
Propranolol	0	+	+	impaired	+
Propranolol LA ...	0	+	+	impaired	+
Timolol	0	+	+	impaired	+

E. Indications

Indications 19.2%	Weight factor	Angina Pectoris	Myocardial Infarction	Cardiac Arrythmia	Migraine
Acebutolol	25			L*	
Atenolol	50	L			U
Carteolol	25	U			
Labetalol	0				
Metoprolol	75	L	L		U
Nadolol	25	L			U
Penbutolol	0				
Pindolol	0				
Propranolol	90	L	L	L	L
Propranolol LA ...	90	L	L	L	L
Timolol	50		L		U

F. Drug Interactions

Drug Interactions 12.8%	Weight factor	Cimetidine	Sympathomimetics*		
Acebutolol	75	0	0		
Atenolol	75	0	0		
Carteolol	50	0	+		
Labetalol	25	+	+		
Metoprolol	50	+	0		
Nadolol	50	0	+		
Penbutolol	50	0	+		
Pindolol	50	0	+		
Propranolol	25	+	+		
Propranolol LA ...	25	+	+		
Timolol	50	0	+		

V. Scoring Matrix

A. Ivory Tower

Scoring Matrix					Weight Factors		
		Cost	Pkin	Phar	ADR	Ind	DI
Drug	Score	25	75	90	75	75	50
Acebutolol	15.0	25	35	85	85	25	75
Atenolol	15.0	75	80	50	75	50	75
Carteolol	8.4	15	65	35	25	25	50
Labetolol	5.4	90	70	25	0	0	25
Metoprolol	12.9	50	80	50	50	75	50
Nadolol	7.6	75	90	25	0	25	50
Penbutolol	7.5	85	50	15	50	0	50
Pindolol	8.4	25	75	25	50	0	50
Propranolol	6.5	90	10	10	0	90	25
Propranolol LA	7.0	80	30	10	0	90	25
Timolol	5.1	50	15	10	0	50	50

B. Without Cost

Scoring Matrix					Weight Factors		
		Cost	Pkin	Phar	ADR	Ind	DI
Drug	Score		75	90	75	75	50
Acebutolol	15.7		35	85	85	25	75
Atenolol	15.3		80	50	75	50	75
Metoprolol	14.3		80	50	50	75	50
Carteolol	8.8		65	25	25	25	50
Pindolol	8.7		75	25	50	0	50
Nadolol	7.4		50	25	0	25	50
Penbutolol	7.2		50	15	50	0	50
Propranolol LA	6.7		30	10	0	90	25
Propranolol	6.0		10	10	0	90	25
Labetolol	4.9		70	25	0	0	25
Timolol	4.9		15	10	0	50	50

C. Reality Check

Scoring Matrix					Weight Factors		
		Cost	Pkin	Phar	ADR	Ind	DI
Drug	Score	25	0	25	0	75	0
Propranolol	15.9	90		10		90	
Atenolol	15.7	75		50		75	
Propranolol LA	15.3	70		10		90	
Metoprolol	11.5	50		50		50	
Acebutolol	9.3	25		85		25	
Timolol	9.1	50		10		50	
Nadolol	7.3	75		25		25	
Carteolol	6.0	15		35		25	
Labetolol	4.2	90		25		0	
Penbutolol	3.5	85		15		0	
Pindolol	2.2	25		25		0	

VI. Conclusion

Classification: Anxiolytics **Weight Factors: natl p&t**

Drug Comparison Scores

Drug	Score	Drug	Score
Lorazepam	17.8	Oxazepam	4.7
Clorazepate	17.0	Halazepam	4.6
Diazepam	17.0		
Chlordiazepoxide	13.8		
Alprazolam	9.3		
Buspirone	9.3		
Prazepam	6.4		

Drug Comparison Score

Diazepam = 17.0

	Profile Percentage		Within Profile Percentage		
Cost	0	x	0	=	0
Pharmacokinetics	4	x	10.5	=	42
Ease of Use	20	x	15.8	=	316
CNS Effects	30	x	18.4	=	552
Labelled Indications	36	x	20.7	=	745.2
Drug Interactions	10	x	3.2	=	32
	100%				1687.2/100 = 16.9

Classification: Anxiolytics **Weight Factors: natl p&t**

Profile	Weight factor	
Cost		0.0%
Pharmacokinetics	10	4.0%
Ease of Use	50	20.0%
Potential Adverse CNS Effects	75	30.0%
Labelled Indications	90	36.0%
Drug Interactions	25	10.0%

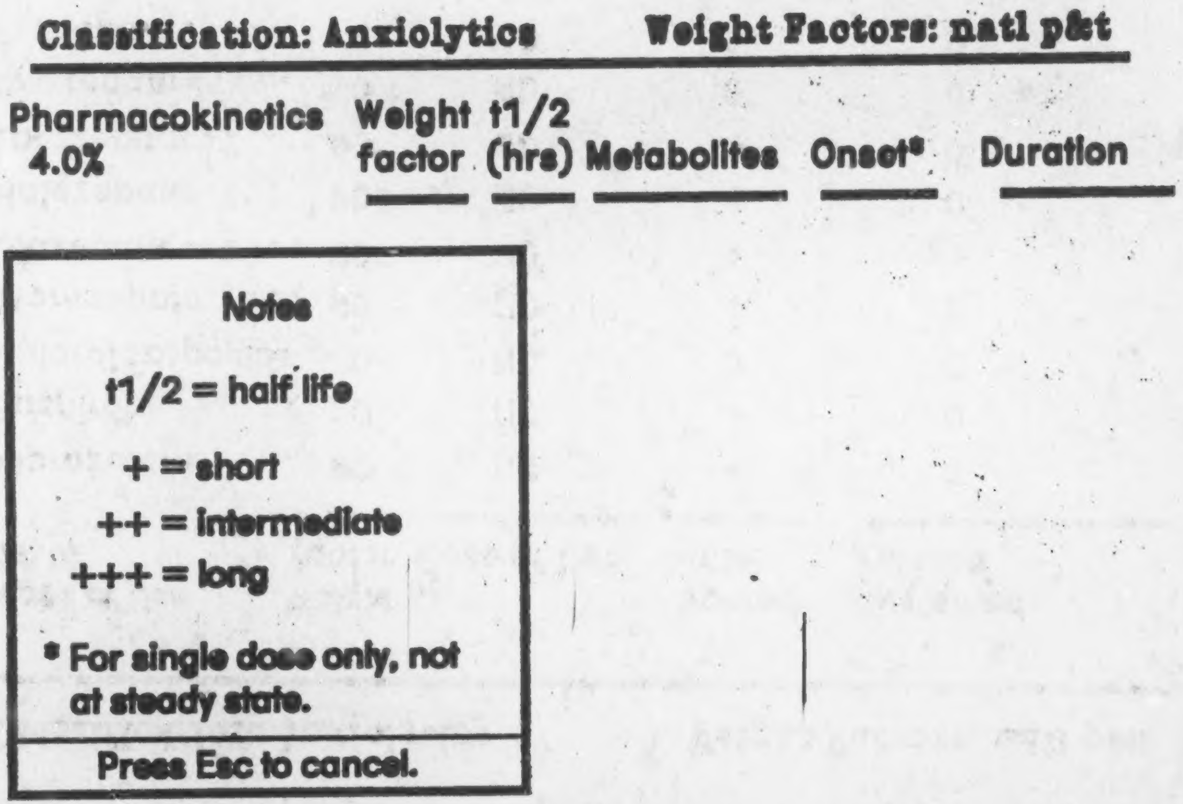
-Percentages based on sum of assigned weight factors.

Classification: Anxiolytics **Weight Factors: natl p&t**

Cost 0.0%	Weight factor	UNL adult dose	Cost/Month AWP*	Cost/Month Actual
Alprazolam	50	0.50 mg tid	35.10	
Buspirone	25	10 mg tid	58.50	
Chlordiazepoxide	75	10 mg tid	21.60	
Clorazepate	50	15 mg tid	42.24	
Diazepam	99	10 mg tid	4.32	
Halazepam	75	40 mg tid	27.00	
Lorazepam	99	1 mg tid	9.90	
Oxazepam	75	15 mg tid	25.07	
Prazepam	25	20 mg tid	55.98	

Classification: Anxiolytics **Weight Factors: natl p&t**

Pharmacokinetics 4.0%	Weight factor	t1/2 (hrs)	Metabolites	Onset[a]	Duration
Alprazolam	10	7 - 15	Active	++	++
Buspirone	90	2 - 3	Active	++/+	+
Chlordiazepoxide	75	5 - 30	Active	++	+++
Clorazepate	60	30 - 100	Active	+	+++
Diazepam	60	20 - 50	Active	+	+++
Halazepam	50	5 - 15	Active	++	+++
Lorazepam	99	8 - 25	Inactive	++	++
Oxazepam	50	5 - 15	Inactive	+++	+/++
Prazepam	75	30 - 100	Active	+++	+++



Classification: Anxiolytics **Weight Factors: natl p&t**

Pharmacokinetics
4.0%

Weight factor	t1/2 (hrs)	Metabolites	Onset*	Duration

Notes

t1/2 = half life

+ = short
++ = intermediate
+++ = long

* For single dose only, not at steady state.

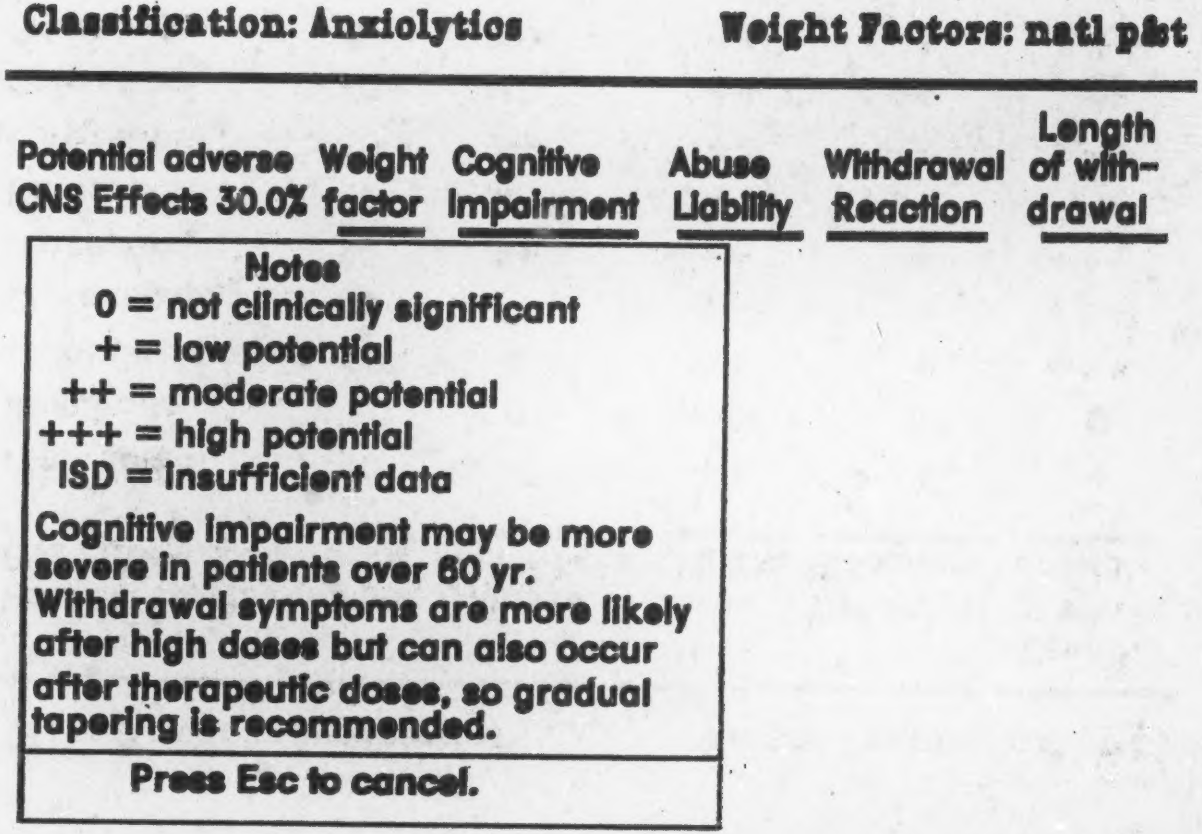
Press Esc to cancel.

Classification: Anxiolytics **Weight Factors: natl p&t**

Ease of Use 20.0%	Weight factor	Ease of Use	Scored tablet	Sustained release	
Alprazolam	90	TID	+	0	
Buspirone	90	TID	+	0	
Chlordiazepoxide	0	TID	0	0	
Clorazepate	90	TID	+	0	
Diazepam	90	TID	+	+	
Halazepam	90	TID	+	0	
Lorazepam	90	TID	+	0	
Oxazepam	0	TID	0	0	
Prazepam	0	TID	0	0	

Classification: Anxiolytics **Weight Factors: natl p&t**

Potential adverse CNS Effects 30.0%	Weight factor	Cognitive Impairment	Abuse Liability	Withdrawal Reaction	Length of withdrawal
Alprazolam	10	+	++	+++	+
Buspirone	50	0	0	0	0
Chlordiazepoxide	90	+	++	+	+++
Clorazepate	90	++	++	+	+++
Diazepam	90	++	+++	+	+++
Halazepam	10	ISD	++	+++	+
Lorazepam	50	++	++	++	++
Oxazepam	10	ISD	++	+++	+
Prazepam	90	ISD	++	+	+++



```
Classification: Anxiolytics                    Weight Factors: natl p&t

                                                                  Length
Potential adverse  Weight  Cognitive    Abuse      Withdrawal  of with-
CNS Effects 30.0%  factor  Impairment   Liability  Reaction    drawal

            Notes
    0 = not clinically significant
    + = low potential
   ++ = moderate potential
  +++ = high potential
  ISD = insufficient data
 Cognitive impairment may be more
 severe in patients over 60 yr.
 Withdrawal symptoms are more likely
 after high doses but can also occur
 after therapeutic doses, so gradual
 tapering is recommended.

       Press Esc to cancel.
```

Classification: Anxiolytics **Weight Factors: natl p&t**

Labelled Indications 36.0%	Weight factor	Anxiety w/depression	Alcohol withdrawal	Muscle relaxant	Anti-convulsant
Alprazolam	50	X			
Buspirone	0				
Chlordiazepoxide	75		X	X	X
Clorazepate	75		X	X	X
Diazepam	75				X
Halazepam	0				
Lorazepam	75	X	X	X	
Oxazepam	12	X			
Prazepam	0				

Classification: Anxiolytics **Weight Factors: natl p&t**

Labelled indications 36.0%	Weight factor	Anxiety w/depression	Alcohol withdrawal	Muscle relaxant	Anti-convulsant

Notes

The following drugs are approved for use in anxiety disorders and the short term relief of those symptoms:

Alprazolam
Buspirone
Chlordiazepoxide
Clorazepate
Diazepam
Halazepam
Lorazepam
Oxazepam
Prazepam

Oxazepam is approved for geriatric use.

Classification: Anxiolytics **Weight Factors: natl p&t**

Drug Interactions 10%	Weight factor	Alcohol&CNS Depressants	Cimetidine (* others)	MAO Inhibitors	Digoxin
Alprazolam	10	+	+	0	+
Buspirone	70	0	0	+	+
Chlordiazepoxide	10	+	+	0	+
Clorazepate	10	+	+	0	+
Diazepam	10	+	+	0	+
Halazepam	10	+	+	0	+
Lorazepam	99	+	0	0	+
Oxazepam	80	+	0	0	+
Prazepam	10	+	+	0	+

Classification: Anxiolytics **Weight Factors: natl p&t**

Drug Interactions 10%	Weight factor	Alcohol&CNS Depressants	Cimetidine (* others)	MAO Inhibitors	Digoxin

Notes

+ = Clinically significant

0 = Not clinically significant

* other drugs with same interactions

- Ketoconazole
- Valproic acid
- Metoprolol
- Erythromycin

Drug interaction is dependent on dose and at low doses may not be clinically significant.

Classification: Anxiolytics **Weight Factors: natl p&t**

Scoring Matrix / Weight Factors

Drug	Score	Cost	Pkin	Ease	CNS	FDA	DI
			10	50	75	90	25
Lorazepam	17.8		99	90	50	75	99
Clorazepate	17.0		60	90	90	75	10
Diazepam	17.0		60	90	90	75	10
Chlordiazepoxide	13.8		75	0	90	75	10
Alprazolam.	9.3		10	90	10	50	10
Buspirone	9.3		90	90	50	0	70
Prazepam	6.4		75	0	90	0	10
Oxazepam	4.7		50	0	10	12	80
Halazepam	4.6		50	90	10	0	10

Classification: Anxiolytics **Weight Factors: natl pbt**

Scoring Matrix Weight Factors

		Cost	Pkin	Ease	CNS	Ind	DI
Drug	Score	75	10	50	75	90	25
Lorazepam	17.7	99	99	90	50	75	99
Diazepam	17.1	99	60	90	90	75	10
Clorazepate	15.1	50	60	90	90	75	10
Chlordiazepoxide	13.7	75	75	0	90	75	10
Alprazolam.	9.2	50	10	90	10	50	10
Buspirone.	8.2	25	90	90	50	0	70
Oxazepam	6.7	75	50	0	10	12	80
Halazepam	6.6	75	50	90	10	0	10
Prazepam	5.9	25	75	0	90	0	10

DOCUMENTATION OF CLINICAL PHARMACY SERVICES IMPACT IN A NON-STAFF MODEL HMO

by Donna Schmidt and Norrie Wilkins
PARTNERS National Health Plans
Minneapolis, Minnesota

OBJECTIVE

Show a decrease in PMPM (per member per month) drug expenses resulting from clinical pharmacy programs.

GENERALIZABILITY

Estimated Impact of Clinical Services
Can Be Affected By:

1. **Local practice standards.**
2. **Different percent of HMO patients in physicians' population.**
3. **Length of time a physician participates with an HMO.**
4. **Media releases about drugs and drug therapy.**
5. **Severity of illness.**

METHODOLOGY

1. Coverage denied for drugs with little or no therapeutic advantages (AXID, CECLOR capsules) and physician education by newsletter on CECLOR.

2. Coverage denied for certain drug dosage forms (KEFLET, KEFTAB, EMYCIN) and physician education by newsletter on oral antibiotics.

3. Coverage denied for specific convenience units (QUESTRAN packets, CHOLYBAR, INDOCIN SR).

4. Prior authorization and physician education of a specific drug (MEVACOR).

5. Preferred ACE inhibitor in formulary for hypertension (LISINOPRIL).

6. Coverage denied for drugs without proven therapeutic efficacy (NICORETTE).

7. Newsletter to educate physicians on cost effective therapy for NSAIDs (VOLTAREN).

METHODOLOGY I

Comparison of a Health Plan's Experience to a National Standard,

Pharmaceutical Data Service (PDS)

A.

$$\begin{array}{l}\text{Expected number of}\\ \text{PDS Rx for Drug 1}\end{array} = \left[\begin{array}{l}\text{PDS Percent}\\ \text{market share}\\ \text{for Drug 1}\end{array}\right]\left[\begin{array}{l}\text{Plan's total Rx}\\ \text{in therapeutic}\\ \text{class of Drug 1}\end{array}\right]$$

$$\begin{array}{l}\text{Expected number of}\\ \text{PDS Rx for Voltaren}\end{array} = (11\%)\ (15609) = 1717\ \text{Rxs}$$

B.

$$\begin{array}{l}\text{Cost of PDS}\\ \text{Market Share}\end{array} = \left[\begin{array}{l}\text{Expected \#}\\ \text{PDS Rx's for}\\ \text{Drug 1}\end{array}\right]\left[\begin{array}{l}\text{Plan's average}\\ \text{Cost per Rx of}\\ \text{Drug 1}\end{array}\right]$$

$$\begin{array}{l}\text{Cost of PDS}\\ \text{Market Share}\\ \text{for Voltaren}\end{array} = \begin{array}{lrlcr}\text{25mg:} & (38) & (\$16.24) & = & \$617\\ \text{50mg:} & (622) & (\$30.98) & = & \$19{,}270\\ \text{75mg:} & \underline{(1051)} & (\$34.14) & = & \underline{\$35{,}881}\\ & (1717) & & & \$55{,}768\end{array}$$

C. $$\text{Savings for Drug 1} = \left[\text{Cost of PDS} \cdot \text{Market Share}\right] - \left[\text{Cost of Plan's Ingredient Cost}\right]$$

$$\text{Savings for Voltaren} = \$55{,}768 - \$21{,}922\,^{*} = \$33{,}846$$

D. $$\text{PMPM Savings} = \left[\frac{\text{Savings for Drug 1}}{\text{Plan's Member Months}}\right]$$

$$\text{PMPM Savings for Voltaren} = \frac{\$33{,}846}{767{,}516} = \$0.044$$

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* Controlled for Total NSAID Use.

METHODOLOGY II

Comparison of Health Plan A (with Intervention) to Health Plan B (control) by Drug or Therapeutic Class

Example: **Mevacor prior authorization**

Health Plan A

Ingredient cost January - June 1989	$13,080 *
Member Months	195,668
PMPM	$0.0668

Health Plan B

Ingredient cost January - June 1989	$20,568
Member Months	196,812
PMPM	$0.1045

Savings **PMPM = $0.0377**

* Controlled for Total Antilipemic Use

RESULTS

		Methods	
		I	II
1.	Coverage denied for drugs with little or no therapeutic advantages (AXID, CECLOR capsules) and physician education by newsletter on CECLOR.	$.37	
2.	Coverage denied for certain drug dosage forms (KEFLET, KEFTAB, EMYCIN) and physician education by newsletter on oral antibiotics.		$.28
3.	Coverage denied for specific convenience units (QUESTRAN packets, CHOLYBAR, INDOCIN SR).		$.07
4.	Prior authorization and physician education of a specific drug (MEVACOR).		$.04
5.	Preferred ACE inhibitor in formulary for hypertension (LISINOPRIL).	$.08	
6.	Coverage denied for drugs without proven therapeutic efficacy (NICORETTE).		$.09
7.	Newsletter to educate physicians on cost effective therapy for NSAIDs (VOLTAREN).	$.04	
		$.12	$.85